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Neuroendocrine Aspects of Improving Sleep in Epilepsy*

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Abstract

Sleep plays an intricate role in epilepsy and can affect the frequency and occurrence of seizures. With nearly 35% of U.S. adults failing to obtain the recommended 7 hours of sleep every night, understanding the complex relationship between sleep and epilepsy is of utmost relevance. Sleep deprivation is a common trigger of seizures in many persons with epilepsy and sleep patterns play a role in the occurrence of seizures. Some patients have their first seizure or repeated seizures after an “all-nighter” at college or after a long period of chronic sleep deprivation. The strength of the relationship between sleep and seizures varies between patients, but improving sleep and optimizing seizure control can have significant positive effects on the quality of life for all these patients. Research has shown that the changes in the brain’s electrical and hormonal activity occurring during normal sleep-wake cycles can be linked to both sleep and seizure patterns. Many questions remain to be answered about sleep and epilepsy. How can sleep deprivation trigger an epileptic seizure? How do circadian and hormonal changes influence sleep pattern and seizure occurrence? Can hormones or sleeping pills help with sleep in epilepsy? In this article we discuss these and many other questions on sleep in epilepsy, with an emphasis on sleep architecture, hormone changes, mechanistic factors, and possible prevention strategies.

Keywords

Insomnia; sleep; epilepsy; melatonin; antiepileptic; tonic inhibition

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Introduction

The relationship between sleep and epilepsy has long been recognized. In the mid 1880s, William Gowers observed that 21% of epilepsy patients had seizures exclusively at night, while 42% of patients had seizure only during the day (Gowers, 1881). This observation later gave rise to epilepsies defined by their position in the sleep-wake cycle: “wakening epilepsies,” which occur within hours of arousal, or “sleep epilepsies,” which would compromise the 21% of patients Gowers observed over a century ago (Janz, 2000). With the advent of the EEG and improved understanding of sleep stage classifications and their unique electrical discharges, it is evident that the influence of sleep on epilepsy is specific to different sleep stages. Frontal lobe seizures are more prevalent at night and temporal lobe seizures tend to generalize more at night (Herman et al, 2001). Furthermore, when seizures occur out of sleep, they tend to predominate in certain sleep stages (Herman et al, 2001). Similarly, epileptiform discharges predominate in NREM sleep. As discussed below, K-complexes and the high amplitude waves present in the N3 stage of NREM sleep (delta activity) are electrographically similar to epileptic waveforms called interictal spikes (Table 1).

Patients with epilepsy, whether managed with medication or not, often have “breakthrough seizures” due to triggers such as stress, missing medications, or alcohol consumption, but sleep deprivation is the most common of these (Frucht et al., 2000; Ferlisi and Shorvon, 2014; Wassenaar et al., 2014; Cobabe et al., 2015). In epilepsy clinics, sleep deprivation is reported to be the most common trigger for seizures regardless of the type of epilepsy or epilepsy syndrome (Foldvary-Schaefer N, Grigg-Damberger, 2006; Jain and Kothare, 2015). Sleep deprivation, due to a variety of primary sleep disorders like sleep apnea, has been shown to increase seizure frequency (Kataria and Vaughn, 2016; Derry and Duncan, 2013). Although information on the neurobiological characteristics of sleep has advanced in recent years, insufficient knowledge exists on the relationship between sleep disorders and epilepsy, along with a lack of rational strategies for improving sleep quality in persons with epilepsy. This article describes sleep issues in epilepsy, with an emphasis on sleep architecture, hormone mechanisms, risk factors, and possible clinical strategies for alleviating sleep disturbances in epilepsy.

Sleep and Its Disorders

Sleep is a vital physiology activity. With the advent of the electroencephalogram (EEG), sleep is divided into two electrically and physiologically distinct phases: non-rapid eye movement (NREM) and rapid eye movement (REM), respectively (Fig.1). NREM sleep can be further subdivided into N1–N3 (S1–S4). These classifications are based on the observation of distinctive waveforms (Daroff and Bradley, 2012; Miller, 2015; Kryger and Roth, 2017). A sleeping individual typically passes through REM and NREM sleep between four and six times each night with each cycle lasting about 95 minutes, however as one ages, less sleep is required (Daroff and Bradley, 2012). The first two cycles of this process comprise the most slow wave sleep (N3); throughout the night, NREM sleep duration decreases as REM sleep duration increases. NREM sleep makes up between 75% and 80% of sleep for an adult (Moser et al., 2009; Kryger and Roth, 2017). REM sleep therefore

represents 20–25% of total sleep time, first occurring 60–90 minutes after the start of the cycle.

The American Academy of Sleep Medicine (AASM) has published specific guidelines on sleep and wakefulness (Miller, 2015; Ilber et al., 2007; Miller, 2015). As mentioned previously, wakefulness and the different stages of sleep can be distinguished through EEG (Fig. 1). Wakefulness is associated with beta waves, which are low amplitude, desynchronized, high frequency (14–30 Hz) waves. In the transition to a sleeping state, alpha waves activity increases on the EEG. These waves are often referred to as “quiet rest” or “quiet wakefulness” waves. With frequency in the 8–13 Hz range they mark the beginning of sleep (Arrigoni and Fuller, 2012). The first stage of NREM sleep (N1/S1) is then characterized by theta waves, low frequency waves ranging from 4 to 7 Hz. The second phase in the sleep cycle, termed S2/N2 phase, is reached when sleep spindles and K-complexes are observed on the EEG readout. In this phase, the person has lost consciousness. Stages 3 and 4 (S3 and S4, or simply N3) of NREM sleep can be distinguished by delta waves with high amplitudes, greater than 75 μ V, and frequency less than 4 Hz. This phase is termed “deep sleep” and is clinically denoted as slow wave activity. The final stage in the sleep cycle is REM sleep, which is defined by skeletal muscle atonia, activation of the cortex and hippocampus, and frequent dreaming. This phase has sawtooth waves with relatively low voltage.

Sleep disturbances can have profound impact on many neurological conditions and may be indicators for other serious brain conditions (Breslau et al., 1998; Buysse et al., 2008; Mathias and Alvaro, 2012; Im et al., 2016). Insomnia disorder is the most common of the sleep-wake disorders, with one third of adults reporting insomnia-like symptoms and 6%–10% of these people meeting the criteria for insomnia disorder (Ohayon and Reynolds, 2009; Buysse et al., 2008). The most common single symptom of insomnia is difficulty maintaining sleep, but can manifest throughout the sleep cycle (Roth et al., 2006; Barateau et al., 2017). Sleep disturbances are common in many epileptic syndromes. Although a variety of epileptic seizures and epilepsy syndromes cause profound impact on sleep, mechanisms underlying these disturbances are poorly understood. It remains to be explained how sleep deprivation can trigger an epileptic seizure; how do circadian and hormonal changes influence sleep pattern and seizure occurrence; why epileptic seizures are rare in REM sleep; and whether or not hormones or sleeping pills help with sleep in epilepsy. This article outlines these and many other questions on sleep in epilepsy, with an emphasis on sleep architecture, hormone changes, mechanistic factors, and possible prevention strategies. Understanding the neurophysiological correlation of how sleep affects seizures is crucial for designing effective strategies to prevent sleep-related epileptic seizures.

GABA-A Receptors in Sleep and Epilepsy

The neurotransmitter γ -aminobutyric acid (GABA) is the primary inhibitory modulator of neuronal excitability in the brain. GABA acts at two types of receptors: ionotropic GABA-A receptors and metabotropic G protein-coupled GABA-B receptors. Ionotropic GABA-A receptors are membrane-bound, ligand-gated chloride ion channels responsible for the majority of fast neuronal inhibitory transmission in the brain. These GABA-A receptors play

critical roles in sleep and epilepsy (Loup et al., 2000; Wisden et al., 2017). When activated by GABA, GABA-A receptors initiate an influx of negative-charged chloride ions, further polarizing the cell to create an inhibitory current (Baulac et al., 2001). GABA-A receptors are hetero-pentamers made from 19 known subunits (Fig.2). The most prevalent subtypes contain 2α , 2β , and 1γ or δ subunits. The abundance of available subunits and the consequential variety of possible subtype combinations make GABA-A receptors extremely heterogeneous. The composition and distribution of these receptors yield diverse functions across the brain. In the synaptic site, γ subunit-containing GABA-A receptors generate fast and transient phasic currents (known as inhibitory postsynaptic currents, IPSCs) in response to the binding of highly concentrated GABA released presynaptically. In the extrasynaptic site, the major GABA-A receptors contain δ subunits and are responsible for the maintaining basal GABAergic tonic inhibition in the brain. They do so by conducting tonic currents when a low concentration of ambient GABA binds. In the hippocampus, a critical region for seizures and cognitive functions, different subtypes of GABA-A receptors are found in distinct cell types: dentate gyrus granule cells (DGGCs) contain $\alpha3\beta3\gamma2$ and $\alpha4\beta2/3\delta$ receptors in the synaptic and extrasynaptic sites, respectively (Sperk et al., 1997; Peng et al., 2002); cornu ammonis 1 (CA1) pyramidal neurons mainly contain $\alpha5\beta3\gamma2$ receptors, and hippocampal interneurons contain $\alpha1\beta2\delta$ receptors containing (Sun et al., 2004; Glykys and Mody, 2007; Mortensen et al., 2011). The synaptic and extrasynaptic sites of the relay neurons in the center thalamus, which is known to regulate sleep, contain $\alpha1\beta2\gamma2$ and $\alpha4\beta2\delta$, respectively (Jia et al., 2005; Dai et al., 2009). In the thalamic reticular neurons, $\alpha3\beta3\gamma2$ receptors are present. Notably, $\alpha4$ subunits, which are highly expressed in both the hippocampus and thalamus, contribute largely to extrasynaptic tonic inhibition in DGGCs and thalamic relay neurons (Chandra et al., 2006). Such GABAergic inhibition is highly relevant to sleep. Moreover, enhanced thalamic GABAergic inhibition, confers the reduction of thalamic oscillations and absence seizures (Schofield et al., 2009). Similarly, $\alpha5$ -subunits contribute to tonic inhibition in the hippocampal pyramidal cells and neocortical pyramidal cells, while $\alpha6$ subunits contribute extrasynaptic tonic inhibition in the cerebellar granule cells.

GABA-A receptors are primary targets for the treatment of both sleep- and epilepsy-related disorders. Many sleep aids and antiepileptic drugs are positive allosteric modulators (PAM) of GABA-A receptors, including general anesthetics propofol and etomidate (Krasowski et al., 2001; Feng and Forman, 2017), sedative zolpidem (Crestani et al., 2000), benzodiazepines (Reddy et al., 2015), and neurosteroids such as allopregnanolone, ganaxolone, and THDOC. These agents potentiate the function of GABA-A receptors by increasing inhibitory currents and thus decreasing neuronal excitability (Carver et al., 2016; Chuang and Reddy, 2018a; b). Electrophysiological studies have shown that most of the PAMs listed above potentiate phasic inhibition by acting at synaptic $\alpha\beta\gamma$ receptor to prolong IPSC decay time (Feng and Forman, 2017). Except for benzodiazepines, which have limited effects on extrasynaptic receptors, they also potentiate tonic inhibition by acting at extrasynaptic $\alpha\beta\gamma$ receptors. The anesthetic propofol enhances both tonic and phasic currents in neurons of the solitary tract nucleus, in cardiac vagal neurons of the nucleus ambiguus, and in ventral horn interneurons of the spine (McDougall et al., 2008; Wang, 2009; Eckle et al., 2015). In addition, GABA-A receptor-mediated synaptic inhibition is

crucial for the hypnotic effects of propofol in the thalamic specific relay nuclei (Zhang et al., 2013). Etomidate, an anesthetic selective for $\beta 2/3$ -containing receptors, increases the amplitude of miniature IPSCs in thalamocortical slices and prolongs the decay time of mIPSCs in thalamocortical slices, hippocampal CA1 pyramidal neurons, and in thalamic ventrobasal (VB) neurons (Belelli et al., 2005; Cheng et al., 2006; Dai et al., 2009). It also enhances tonic inhibition by preferentially potentiating $\alpha 5$ -containing receptors in hippocampal CA1 pyramidal neurons (Cheng et al., 2006; Saliba et al., 2012). The hypnotic zolpidem increases the decay time of spontaneous IPSCs in hippocampal interneurons and in VB neurons. Zolpidem also potentiates tonic inhibition in hippocampal interneurons and in neocortical pyramidal neurons but not in VB neurons (Jia et al., 2005; Yamada et al., 2007; Song et al., 2011). Neurosteroids are preferential PAMs of subunit-containing receptors in recombinant receptors as well as in native hippocampal neurons (Chuang and Reddy, 2018a). The neurosteroid HDOC was previously reported to increase durations of evoked IPSCs and spontaneous IPSCs in thalamic VB neurons (Porcello et al., 2003). However, the effects of neurosteroids on extrasynaptic tonic inhibition of the thalamic network are not well understood.

Innovative Therapeutic Approaches for Sleep in Epilepsy

Sleep and circadian rhythm disturbances in epilepsy

Sleep disturbances ranging from insomnia and hypersomnia are commonly reported by patients with epilepsy. Moreover, whether epilepsy is controlled with medication or not and regardless of the type of epilepsy syndrome, sleep deprivation is frequently reported as a trigger for “breakthrough” seizures (Ferlisi and Shorvon, 2014; Obabe et al., 2015). In fact, sleep disruption is used in epilepsy monitoring units to trigger seizures and increase diagnostic EEG yield (Foldvary-Schaefer and Grigg-Damberger, 2006; Jain and Kothare, 2015). While sleep deprivation may trigger seizures, seizures themselves can also disrupt sleep even in patients whose seizures are well-controlled. Seizures have circadian distribution in different epilepsy syndromes in humans, and similar circadian seizure distribution has been shown in animal models (Ramgopal et al., 2012; Van Nieuwenhuyse et al., 2015; Wright et al., 2016). Moreover, several studies have shown that both diurnal and circadian rhythms as well as sleep-wake patterns are disrupted in humans and animal models (Fenoglio-Simeone et al., 2009; Stewart et al., 2001; Bazil et al., 2000; Nakamura et al., 2017; Boly et al., 2017). Thus sleep and seizures potentiate each other as part of a vicious cycle in which seizures disrupt both sleep and circadian rest-activity rhythms, and disrupted sleep increases seizures, a positive feedback cycle that may contribute to disease progression. Understanding the mechanisms underlying these interactions may have therapeutic implications.

Circadian rhythm disturbances in *Kv1.1^{-/-}* mouse model

While prior studies have demonstrated that sleep disruptions are common in epilepsy, we sought to examine how circadian and diurnal rhythms are disrupted in the *Kv1.1^{-/-}* mouse model of epilepsy. Using actigraphy, we found that epileptic *Kv1.1^{-/-}* animals have drastically disrupted diurnal and circadian rest-activity patterns (Fig.3) as well as a prolonged circadian period compared to wild types (WT). Sleep analysis showed that

epileptic mice spend more time awake and less time in NREM sleep (Fig.3). In addition, the characteristics of sleep and wake bouts for Kv1.1^{-/-} (KO or Kcna1^{-/-}) mice are significantly altered compared to wildtype (Kcna^{+/+} or WT) littermates, regardless of lighting conditions (Wallace et al, 2018). In another study, we found that all Kv1.1KO animals died between P45 and 70. Furthermore, while no difference in “rest” values was evident between KO and WT controls at P26, starting at ~P38, the number of rest epochs prior to mortality in KO mice was prominently and progressively reduced. Conversely, no change in rest-activity patterns was seen in WT controls for the duration of experiment (Fig. 3) (Iyer et al., 2018).

Clock gene and Sirt1 oscillation is reduced in Kv1.1^{-/-} mice

Mammalian circadian rhythms are regulated by a pacemaker that operates with a periodicity of ~24 hours that can sustain even in the absence of zeitgebers (typically light in mammals). Sleep is the most obvious circadian behavior, but many other physiological processes are under circadian regulation. In addition to tissue-specific rhythmicity, coordination between systems is regulated by a central pacemaker in the suprachiasmatic nucleus (SCN) of hypothalamus, a relatively small cluster of GABAergic neurons that are capable of integrating environmental, emotional and metabolic inputs (Welsh et al, 2010). Central to its function is a transcriptional-translational feedback loop (TTFL) of Clock genes, namely Bmal1, Clock, Per1–3 and Cry1/2) (Ye et al, 2011). Transcription is promoted when CLOCK:BMAL1 dimerize and binds to E-box promoter sites of Per and Cry (positive loop). Per and Cry are translated and upon reaching a critical concentration point, they dimerize and translocate into the nucleus where they repress the transcriptional drive by interacting with the CLOCK:BMAL1 complex(negative loop). The positive and negative loops of TTFL drive rhythmic expression of the Clock genes and the downstream oscillating behavioral rhythms (Ye et al, 2011). Sirt1 is a nicotinamide (NAD⁺) dependent Hde-AC that itself is expressed in a circadian manner and is critically involved in both the positive and negative loops of the TTFL. In the positive loop of TTFL transcriptional arm, Sirt1 counteracts the histone acetyltransferase activity of Clock and acetylation of specific residues in BMAL1, and effecting CLOCK:BMAL1 interaction (Asher et al, 2008; Wang et al, 2016) . In the negative loop, Sirt1 exerts a repressive control on clock genes by de-Ac Per2 and in an interconnecting loop de-Ac PGC-1 α , inhibiting CLOCK:BMAL1 complex (Chang and Guarente, 2013). The functional importance of these genes is under investigation.

The role of clock gene and sirt1 oscillation has been investigated in Kv1.1 knockout mice. First, we examined whether seizure frequency correlated with the disrupted rest-activity rhythms but no correlation was found. We then we explored whether aberrant circadian machinery was a factor. We investigated transcript levels of Clock controlled genes (i.e., Bmal1, Clock, Per1, and Per2) inKv1.1^{-/-} and wild-type mice using rt-PCR techniques. In diurnal conditions, we found that all genes except Bmal1 had significant oscillations, indicated by a time main effect across ZT points (Fig.4C) Clock (Fig.4E) Per1 (Fig.4G) Per2. Additionally, we found a main effect of genotype on the diurnal expression of Clock (Fig.5) Per1 (Fig.4E) and Per2 (Fig. 4G) transcripts, where mean transcription was decreased in Kv1.1^{-/-} mutants as compared to WT littermates. Because the expression of several Clock genes is diminished in Kv1.1^{-/-} mice, mimicking the aging condition where Sirt1 levels were decreased (Chang and Guarente, 2013), we sought to determine if aberrant

irt1 expression occurs in these mice. This would potentially cause downstream effects on clock gene expression. Indeed, we found that diurnal expression of Sirt1 had significant oscillations (Fig.5A) and mutant expression of Sirt1 mRNA was lower than WT under diurnal conditions (Wallace et al 2018).

Sleep disturbances are associated with altered GABAergic tonic inhibition

GABAergic tonic inhibition is normally regulated by $\alpha 5$ and δ subunit-containing GABA-A receptors both in the hippocampus (an important region for seizures) and in the thalamus (the brain region regulating sleep) (Glykys et al., 2008;Herd et al., 2009). Previous research has associated decreased tonic inhibition with increased excitability; reduction in $\alpha 5$ and δ subunit-containing GABA-A receptors has been shown in the CA and DG of the hippocampus in mouse models of temporal lobe epilepsy (Peng et al., 2004; Houser et al., 2012). Altered tonic inhibition in the thalamus has been shown to be associated with altered sleep homeostasis; drugs that enhance tonic also enhance NREM EEG delta power (Winsky-Sommerer, 2009). In addition, we found that sleep deprivation reduces expression of both $\alpha 5$ and δ subunit-containing GABA-A receptors in the hippocampus (Fig. 6). Thus, if both seizures and sleep deprivation reduce these subunits, it is likely that reduced tonic inhibition may be the detrimental cyclic relationship between sleep and seizures. If true, targeting $\alpha 5$ and δ subunit-containing GABA-A receptors (where neurosteroids act) in epilepsy may have implications for both seizures and sleep. Diminished tonic currents were evident in the dentate gyrus of normal C57BL6 mice following sleep deprivation (Fig.7). Similar reductions in tonic currents were seen in the Kv1.1 $^{-/-}$ mouse model (Fig.7).

Drugs that enhance tonic inhibition improve sleep and survival

With tonic inhibition already diminished in epilepsy, it is possible that the further reduction of tonic inhibition via sleep deprivation underlies seizure exacerbation. If this is the case, drugs that enhance tonic inhibition, such as neurosteroids, may prevent this phenomenon. Therefore, we sought to determine whether ganaxolone, a PAM of δ containing-subunit of GABA-A receptors improves sleep, seizures and survival in Kv1.1 $^{-/-}$ mice. Compared to untreated mice, sleep significantly improved following ganaxolone treatment (Fig 8B); however, there was no statically significant improvement in seizures (5.5 ± 2.57 vs 4.5 ± 2.35) (Fig 8A). The Kv1.1 $^{-/-}$ mice typically die somewhere between P45 and 70 in our lab experience and we explored whether ganaxolone prolongs survival. When ganaxolone was administered daily starting at P30 at about 10 am each day (single daily dose) under diurnal conditions. It improved the overall survival compared to vehicle control group (mean of 58 days for ganaxolone treated mice; n=11 and 51 days for vehicle treated mice; n=10), though it did not reach significance at the time experiments concluded (Fig 8C).

Emerging Clinical Aspects of Sleep in Epilepsy

Sleep complaints are common in persons with epilepsy, often regarding both excessive daytime sleepiness and poor sleep quality. Though underlying causes are multifaceted, improvement in sleep quality is important for seizure control and quality of life. Antiepileptic drugs (AED) are currently the mainstay for treatment of epileptic seizures (Reddy, 2014). Some adjunct medications can also help in improving sleep quality.

Prevalence of insomnia in epilepsy

There is an increased incidence of sleep disorders amongst persons with epilepsy. Prevalence of obstructive sleep apnea (OSA) is estimated to be as high as 10.2% in adults with epilepsy and as high as 30% in patients with medically refractory epilepsy (Manni et al., 2003; Malow et al., 2000). In addition, older patients with OSA have been found to have worse seizure control than patients without OSA (Chihorek et al., 2007). Conversely, treatment of OSA in persons with epilepsy is associated with improved seizure control (Lin et al., 2017). This bidirectional relationship between OSA and epilepsy mandates consistent screening for OSA amongst patients with epilepsy.

Insomnia is also common in persons with epilepsy. The prevalence is estimated to be between 24–55%. In one survey of over 200 patients, 43% reported clinically significant insomnia and 51% reported at least mild insomnia. Insomnia is also associated with poor seizure control, lower quality of life, and increased health care utilization (Quigg et al., 2016). It is of note that insomnia not only correlates with seizure control, but with other disorders as well. Mood disorders consistently confound reports of insomnia, and in a survey of persons with epilepsy, insomnia severity correlated with depressive symptoms (Yang et al., 2016).

Antiepileptic therapeutics for sleep in epilepsy

Epilepsy treatment (AEDs in particular) can have a significant impact on sleep quality (Table 2). A sleep center study examined the impact of single AEDs on sleep architecture among 39 patients over 72 nights, compared to controls. Carbamazepine and lamotrigine had no significant effect on sleep architecture while phenytoin increased N1 sleep and decreased slow wave and REM sleep, which would be associated with decreased quality of sleep. Valproate also increased N1 sleep. Gabapentin, on the other hand, increased overall slow wave sleep (Legros and Bazil, 2003). A comprehensive review examined the impact of individual AEDs on sleep quality, as measured by objective sleep data. Sleep latency was reduced by phenobarbital, phenytoin and gabapentin, which may be associated with increased sleepiness. Slow wave sleep was increased by carbamazepine, pregabalin, and gabapentin, but decreased by levetiracetam and ethosuximide. REM was reduced by phenobarbital and phenytoin. Arousals were reduced with phenobarbital and gabapentin, but augmented by ethosuximide and gabapentin. Topiramate and lamotrigine were not found to have any definite impact on sleep (Jain and Glauser, 2014).

The relationship between treatment for epilepsy and sleep is not limited to pharmacological therapies (Table 2). In a study of 18 children, initiation of the ketogenic diet was associated with decreased total sleep, but improved overall sleep quality. In addition, daytime sleep was reduced and attentional behavior was improved (Hallbook et al., 2007). While improvement in seizure control likely plays a role in sleep quality, the treatments themselves can also be associated with changes in sleep quality. Sleep quality after epilepsy surgery correlates with clinical outcomes. Among 17 patients that underwent polysomnogram before and after epilepsy surgery, those patients with good outcomes had a significant increase in total sleep time, and a decrease in arousal indices (Zanzmera et al., 2013).

There are some studies on the impact of vagus nerve stimulation (VNS) on sleep (Table 2). Generally patients tell that VNS does not affect their sleep, but there are positive and negative issues from clinical reports. A study of 15 patients found it increased sleep latency, suggesting decreased daytime sleepiness (Malow et al., 2001). A polysomnography (PSG) study in 15 children after VNS placement showed increased slow wave sleep and decrease in sleep latency (Hallbook et al., 2005). PSGs have demonstrated increases in apnea-hypopnea indices after placement of VNS (Marzec et al., 2003; Parhizgar et al., 2011).

Melatonin for sleep in epilepsy

Melatonin is involved in the regulation of sleep-wake cycles. Sold over the counter in the United States, Canada, and some European countries, it is sometimes used as a short-term remedy for sleep disorders. As a pill, it is used for the treatment of insomnia; however, scientific evidence is insufficient to demonstrate benefit in this area (Auld et al., 2017; Li et al., 2018; Burgess and Emens, 2018).

Despite inconclusive evidence for its therapeutic potential, strong interest exists for using melatonin to improve sleep in persons with epilepsy. Many studies have examined the effect of melatonin on sleep induction and sleep quality in patients with epilepsy. A small, randomized trial studied 11 children with epilepsy, patients were treated with 9 mg of sustained-release melatonin or placebo. Over a four-week treatment period, those patients treated with melatonin had significantly reduced sleep latency and wakefulness after sleep onset. Both of these parameters are associated with improved sleep quality (Jain et al., 2015). Melatonin and sleep deprivation were equally efficient in inducing sleep in children with epilepsy (Gustafsson et al., 2015). Melatonin induced sleep may have advantages, especially in younger children as they fall asleep easier than other methods. Overall, melatonin can help improve sleep quality without causing significant side effects.

Sleep hygiene in epilepsy

Sleep hygiene also requires attention. Surveys have shown inadequate sleep hygiene in some persons with epilepsy, which is associated with lower quality of life scores, and more symptoms of anxiety and depression (Manni et al., 2000; Lee et al., 2015). Education regarding interventions to improve sleep hygiene could potentially improve sleep quality. Sleep quality and epilepsy are closely related; improvement of one can potentially be directly correlated with control of the other. In addition to improving seizure control, epilepsy treatments can have direct impact on sleep quality and daytime sleepiness. This variable should be considered when deciding on a treatment for an individual patient. As mentioned earlier, a close relationship also exists between sleep disorders such as OSA and epilepsy. Treatment of OSA can improve seizure control, and given the high incidence of OSA in epilepsy, screening for OSA should be routine. Interventions, such as melatonin supplementation and sleep hygiene, have potential to improve sleep quality, and should be discussed with patients. Finally, insomnia, sleep hygiene and mood disorders are closely related, requiring that all three be addressed to improve quality of life and seizure control.

Conclusions and Future Perspectives

Sleep plays a vital and complex role in the pathophysiology of epilepsy. The problematic occurrence of seizures at night or other unpredictable times is still a major concern for many patients with epilepsy. During the last two decades, many advances have been made in understanding the clinical and electrophysiological aspects of sleep and its impact on epileptic seizures. The bidirectional relationship between epilepsy and sleep has been known for centuries, even before scientific evidence proved that sleep disorders pose a major problem for people with epilepsy. Insomnia is extremely common in persons with epilepsy with an estimated prevalence of 24–55%. Insomnia is associated with poor seizure control and low quality of life. While poor sleep can negatively affect the seizure threshold and the occurrence or frequency of seizures, nighttime seizures can also detrimentally impact quality of sleep. With about 25% patients experiencing seizures only at night, this is a major issue. Many specific epilepsy syndromes are associated with seizures occurring only at certain times in the sleep clock. Sleep complaints are common in persons with epilepsy- including both excessive daytime sleepiness and poor sleep quality. However, the underlying causes are likely multifactorial, especially considering that, AEDs can also influence sleep and sleepiness. By controlling seizures, AEDs can improve the sleep quality. Alternately, improving sleep has been noted to drastically improve seizure control in epilepsy. Melatonin may help to improve sleep quality without causing significant side effects. Insomnia, sleep hygiene and mood disorders are closely related.

Current research is focused on gaining a mechanistic understanding of the interaction between seizures and sleep. Despite decades of research on sleep and seizures, the cellular and molecular mechanism that underlie the vicious cycle of sleep and epilepsy are poorly understood. Future research will advance our understanding of sleep and epilepsy through multidisciplinary approaches and will ultimately translate to significant clinical help for patients. In this article, we described how both sleep and circadian rhythms are disrupted in both humans and in mouse models of epilepsy. Seizures alone cannot account for these disruptions as other mechanisms such as altered expression of clock genes and the epigenetic regulator Sirt1 may underlie these disturbances. Moreover, GABAergic tonic inhibition, a target of neurosteroids has relevance to sleep and epilepsy. Specifically, targeting GABAergic tonic inhibition may be a potential novel approach to rescue sleep in epilepsy. Restoration of sleep and circadian rhythms may have therapeutic potential in delaying disease progression, when not properly managed, sleep disturbances and seizure potentiate each other in a vicious cycle.

While a strong relationship exists between sleep and sudden unexpected death in epilepsy (SUDEP), understanding of the neurobiological aspects of sleep and SUDEP is limited. Targeted basic research using clinically relevant models will provide greater understanding of the cellular, molecular, and systems-level mechanisms that underlie the relationship between sleep and epilepsy.

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Highlights

- Sleep deprivation is a common trigger of seizures in persons with epilepsy.
- However, the underlying causes are poorly understood.
- Neurosteroid-sensitive tonic inhibition has relevance to sleep and epilepsy.
- Insomnia is also common in persons with epilepsy.
- Some adjunct medications like melatonin can help improving sleep quality.

Fig. 1.
Representation of sleep stages with corresponding EEG activity traces (Arrigoni and Fuller, 2012).

Fig. 2. GABA-A Receptor Structure and GABAergic synapse.

(A) A top view of pentameric GABA-A receptor. There are 19 known subunits: α 1–6, β 1–3, γ 1–3, δ , ϵ , θ , π , ρ 1–3. The most common combination contains 2 α s, 2 β s and 1 γ ; the γ subunit can be replaced by δ , ϵ , θ , or π . (B) GABA-A receptors belong to the cys-loop family of ligand-gated ion channels. Each GABA-A receptor subunit contains four transmembrane domains (TM1–4) and one extracellular N terminal and one intracellular C terminal. (C) In GABAergic synapse, GABA is released from the presynaptic neuronal terminal and acts at synaptic and extrasynaptic receptors in the postsynaptic neuron, exerting inhibitory phasic and tonic currents, respectively. BZ, benzodiazepine.

Fig. 3. Novel molecular mechanisms of sleep disturbances in epilepsy.

(A) Disrupted activity rhythm in Kv1.1 KO animals under diurnal or constant conditions, measures across several days. (B) Progressive decline in “rest” epochs in KO mice compared to WT controls and KO mice treated with ketogenic diet (KD-KO). (C) Time sent in sleep and wake under diurnal or constant conditions total (above) and each individual day across 10 days of recording (Iyer et al, 2017; Wallace et al, 2018).

Fig. 4. Expression of clock genes in experimental model.

Transcript levels of four clock genes (*bmal1*, *clock*, *per1* and *per2*) were measured at four time points (ZT 0, 6, 12 and 18) in diurnal (A, C, E, G) and constant conditions (B, D, F, H) in *Kv1.1* KO and wild-type mice (n=3–4 each/genotype/time point/lighting condition and 2 replicates) (Wallace et al, 2018).

Fig. 5. Sirt1 transcription in experimental model.

Sirt 1 expression patterns of Kv1.1^{-/-} (KO) and wild-type (WT) (n=3–4 per genotype/time point/lighting condition and 2 replicates) (Wallace et al, 2018).

Fig. 6. Alterations in GABA-A receptor subunit expression following sleep disturbance.
Note reduced α₅ and δ subunit mRNA. Data represents mean ± SEM (n=5–6 per group).

Fig. 7. Relationship between sleep deprivation and tonic currents.

Acute sleep deprivation (4 hours, A-D) significantly diminishes frequency of mIPSCs and the magnitude of tonic $GABA_A$ currents in normal mice. E) $Kv1.1^{-/-}$ also show reduced tonic inhibition.

Fig. 8. Effect of tonic inhibition promoting drug ganaxolone on sleep.

(A) Differences in seizure frequency with and without ganaxolone. (B) Sleep data at baseline and with ganaxolone. (C) Survival data with and without ganaxolone for 60 day observation period.

Table 1.

The relationship between sleep and epilepsy.

<i>Sleep Stage</i>	<i>Effect on Interictal Discharge</i>	<i>Effect on Seizure</i>
NREM	More common, more distributed	Increase seizure propagation
REM	Less common, less distributed	Partial seizure protection: decrease seizure initialization and propagation
Arousal	Discharges just prior or during	Can initiate seizure or be part of seizure

Table 2.

Impact of epilepsy treatment on sleep.

<i>Improved Sleep Quality</i>	<i>Decrease in Sleep Quality</i>
Gabapentin <ul style="list-style-type: none"> • Increase in slow wave sleep 	Phenytoin <ul style="list-style-type: none"> • Increased sleepiness
Carbamazepine <ul style="list-style-type: none"> • Increase in slow wave sleep 	Valproate <ul style="list-style-type: none"> • Increased drowsiness
Pregabalin <ul style="list-style-type: none"> • Increase in slow wave sleep 	Phenobarbital <ul style="list-style-type: none"> • Increased sleepiness • Decreased REM sleep
Tiagabine <ul style="list-style-type: none"> • Increase in slow wave sleep 	Ethosuximide <ul style="list-style-type: none"> • Decreased slow wave sleep • Increased arousals
Ketogenic Diet <ul style="list-style-type: none"> • Improved sleep quality • Decrease in daytime sleep 	Clobazam <ul style="list-style-type: none"> • Reduces SWS and REM sleep
Epilepsy Surgery <ul style="list-style-type: none"> • Improved, if good seizure outcome 	Levetiracetam <ul style="list-style-type: none"> • Decreases daytime wake times
Vagus Nerve Stimulation <ul style="list-style-type: none"> • Decrease in daytime sleepiness 	Vagus Nerve Stimulation <ul style="list-style-type: none"> • Potential to worsen obstructive sleep apnea
Parampanel <ul style="list-style-type: none"> • No impact on sleep quality of daytime sleepiness 	