Basic Mechanisms of Sleep and Epilepsy

Saurabh R. Sinha

Abstract: The existence of a relationship between epilepsy and sleep has been realized since ancient times. Despite extensive clinical observations and experimental investigations, the precise nature of this relationship however remains unclear and the mechanisms responsible for this are poorly understood. In this study, the authors review the neurophysiology of sleep, concentrating on the various oscillations and electrographic activities associated with different stages of sleep. The authors also review how sleep affects both epileptic seizures and interictal epileptiform discharges. Finally, they discuss the mechanisms, both confirmed and theoretical, which are thought to be responsible for the effect of sleep on epileptic seizures and epileptiform discharges.

Key Words: Sleep, Epilepsy, Basic mechanisms.

Epileptic seizures are the result of abnormal, paroxysmal brain activity. Sleep is accompanied by major changes in the physiology and activity of the brain (and the entire body). Thus, it should not be surprising that sleep has an effect on epileptic seizures. The existence of a relationship between sleep and epilepsy has been recognized since antiquity (Grigg-Damberger and Damberger, 2002), including the observations that some patients had seizures only in their sleep and that sleep deprivation could trigger seizures.

More precise observations regarding timing of seizures (mainly of convulsive and/or generalized tonic-clonic seizures) with respect to the time of day were made in institutionalized patients in the late nineteenth century. From these studies, it became clear that the relationship between sleep and epilepsy is not a simple or homogeneous one. Gowers (1885) subdivided patients with epilepsy into three groups: those with mainly nocturnal seizures, those with mainly daytime seizures, and those in whom seizures occurred randomly throughout the sleep-wake cycle. Those with mainly nocturnal seizures had two main periods of increased seizure activity, at the onset of sleep and at the end of sleep (Gowers, 1885; Langdon-Down and Brain, 1929). Janz (1962) studied >2,000 patients in an outpatient clinic with “major attacks,” presumably mainly generalized tonic-clonic seizures. He also divided patients into categories of awakening epilepsies (those with seizures mainly upon awakening), sleep epilepsies (those with seizure mainly during sleep), and diffuse epilepsy (those without a significant diurnal variation in their seizures). He further recognized that patients with different patterns of seizure distribution during the sleep-wake cycle actually had different seizure characteristics [reviewed by Mendez and Radtke (2001)]. The awakening epilepsies were mainly primary generalized epilepsies with onset in childhood, whereas sleep epilepsies were more likely to be focal and either idiopathic or symptomatic with onset in adolescence or early adulthood. The diffuse epilepsies were most likely to be symptomatic cases and typically had a poorer prognosis.

With the advent of EEG, the understanding of both sleep physiology and seizure pathophysiology exploded. Sleep was recognized to be made up of distinct components, nonrapid eye movement (NREM) sleep (stages 1–4) and rapid eye movement (REM) sleep, each with their own unique patterns of neuronal activity and physiologic changes. NREM is associated with synchronized activity across large areas of the brain, including well-defined EEG oscillations such as sleep spindles, delta waves, and slow cortical oscillations. REM is associated with a relatively desynchronized EEG, resembling the waking state, but with atonia and REMs. With this improved understanding of sleep, it has become clear that beyond the fact that different types of epilepsy syndromes and epileptic seizures react with sleep in different ways, even the different stages of sleep can differently affect seizures. Thus, there are many potential factors related to both epileptic seizures and sleep that could affect the interaction between sleep and epilepsy. These factors are summarized in Table 1. Theoretical mechanisms for these interactions include shared neuronal circuits for sleep and epileptiform activity, the increased synchronization of neuronal activity that is seen with certain stages of sleep, and more complex interactions that depend on the intrinsic physiologic and pathophysiologic characteristics of the epileptic focus or brain and how they are affected by sleep-related activity.

We will start our discussion with a review of normal sleep physiology with an emphasis on the synchronized discharges and oscillations that occur during sleep. Then, we will review observations regarding the effect of sleep-related activity on both interictal and ictal epileptiform activity. Finally, we will discuss known and theorized mechanisms for these interactions.

NORMAL SLEEP PHYSIOLOGY

Early ideas about sleep suggested that it was a state of relative brain inactivity brought about by a lack of sensory input. However, with the advent of EEG and recordings directly from neurons in the brain, it became clear that sleep was not a state of brain inactivity, but rather a complex state that comprised distinct stages (i.e., NREM and REM sleep) each with their own patterns of neuronal and brain activity. Initial experiments with transection of the brain stem in cats and ictal epileptiform activity. Finally, we will discuss known and theorized mechanisms for these interactions.

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103
Our current understanding of the circuits and neurons involved in the generation of wakefulness and sleep suggests a complex interplay among many regions of the brain, especially in the upper brainstem, including the diencephalon and the basal forebrain [for review see the study by Pace-Schott and Hobson (2002)]. The switch between sleep and waking is located in the forebrain [for review see the study by Pace-Schott and Hobson (2002)]. The switch between sleep and waking is thought to be due to activation of cholinergic nuclei in the brainstem leading to activation of thalamocortical cells. Cortical projections from the posterior hypothalamus and basal forebrain. The RAS consists of several subtypes of neurons, including cholinergic (in the laterodorsal tegmental and pedunculopontine tegmental nuclei), noradrenergic (in the locus coeruleus), serotonergic (in the dorsal raphe nuclei), and dopaminergic (in substantia tegmental nuclei), noradrenergic (in the locus coeruleus), serotonergic (in the dorsal raphe nuclei), and dopaminergic (in substantia nigra and the ventral tegmental area) neurons. During wakefulness, there is tonic activity of many components of the RAS. The transition between wakefulness and sleep is thought to result from both passive withdrawal of external stimuli from the RAS and the activation of the preoptic area of the hypothalamus.

There is a complex interplay between firing patterns of different neuronal subtypes releasing various neurotransmitters that lead to the waking state, NREM sleep, and REM sleep. With the reduction of inputs from the RAS and the lateral hypothalamus, there is a widespread increase in GABAergic activity in the brain and brainstem. At the level of the thalamus and cortex, this leads to the emergence of oscillatory activity related to sleep such as spindles, delta waves, and slow oscillations (discussed below). In REM sleep, RAS neurons releasing serotonin or norepinephrine remain inactive, however, cholinergic neurons become active (likely as a result of decreased inhibition from serotonergic and adrenergic inputs). This selective activation of the cholinergic system and its effect on the thalamocortical system leads to a desynchronized (like waking) EEG but with atonia and REMs. The transition from sleep to waking is thought to be due to activation of cholinergic nuclei in the brainstem leading to activation of thalamocortical cells. Cortical cells are activated indirectly both through glutamatergic connections from thalamocortical cells and through projections from the brainstem cholinergic nuclei to the cholinergic neurons in the basal forebrain, which in turn project to the cortex.

**NORMAL SLEEP RHYTHMS AND THEIR GENERATION**

In understanding the relationship between sleep and epilepsy, much attention has been paid to the electrographic correlates of sleep and epilepsy and how they may relate to each other. The EEG during wakefulness and REM sleep consist of relatively faster frequencies and a desynchronized pattern. During NREM sleep, there is an increasing degree of synchronization of neuronal activity, resulting in widespread patterns of relatively synchronous EEG phenomena such as sleep spindles, delta activity, and cortical slow oscillations. Beyond the different stages of NREM sleep, there is a smaller level of organization consisting of alternative periods of relative arousal and quiescence, termed the cyclic alternating pattern (CAP).

Sleep spindles consist of 10 to 14 Hz activity typically lasting 2 to 3 seconds and occurring every 3 to 10 seconds during NREM sleep, especially in stages 2 and 3. In adults, they are seen most commonly over the central regions, near electrodes C3 and C4 of the International 10/20 system. In children, slower (10–12 Hz) spindles that are more prominent anteriorly were observed. The reticular nucleus of the thalamus (RE) and its connection to the dorsal thalamus seems to be responsible for generating sleep spindles. Thalamic relay neurons isolated from the RE do not demonstrate sleep spindles (Steriade et al., 1985) and the anterior nucleus of the thalamus in cats, which does not receive inputs from the RE and does not have spindles (Pare et al., 1987). Isolated portions of the RE can still generate spindle oscillations suggesting a pacemaker role (Steriade et al., 1987). The spindle oscillation generated in the RE cells is transferred to thalamocortical relay cells in the dorsal thalamic nuclei through GABAergic synapses, producing inhibitory postsynaptic potentials (IPSPs) in these cells. These IPSPs lead to de-inactivation (i.e., hyperpolarization of the neuron allows these neurons to play a role in the delta oscillation. The delta oscillation (1–4 Hz) has been demonstrated to survive after thalamectomy (Steriade et al., 1993b). The thalamic component is thought to result from an interplay between intrinsic currents of thalamocortical relay neurons, a hyperpolarization activated cation current, \(I_h\), and a low-threshold \(Ca^{2+}\) current, \(I_{Ca}\). The thalamic component can be synchronized by projections from the cortex, which excite RE cells.

### TABLE 1. Sleep- and Seizure-Related Factors That May Affect the Relationship Between Sleep and Epilepsy

<table>
<thead>
<tr>
<th>Sleep-Related Factors</th>
<th>Seizure-Related Factors</th>
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</thead>
<tbody>
<tr>
<td>Changes in excitability during sleep</td>
<td>Epilepsy syndrome</td>
</tr>
<tr>
<td>Sleep stages</td>
<td>Seizure type</td>
</tr>
<tr>
<td>REM vs. NREM</td>
<td>Focal vs. generalized</td>
</tr>
<tr>
<td>NREM stages 1–4</td>
<td>Location of epileptic focus</td>
</tr>
<tr>
<td>Sleep-related oscillations</td>
<td>Frontal vs. temporal</td>
</tr>
<tr>
<td>Sleep spindles</td>
<td>Underlying pathologic study</td>
</tr>
<tr>
<td>Slow cortical oscillations</td>
<td>Genetic vs. lesional vs. cryptogenic</td>
</tr>
<tr>
<td>Delta oscillations</td>
<td>Types of lesions</td>
</tr>
<tr>
<td>Arousals</td>
<td>Severity of pathologic examination</td>
</tr>
<tr>
<td>K-complexes</td>
<td>Interaction of sleep-related activity with epileptic focus</td>
</tr>
<tr>
<td>Cyclic alternating pattern</td>
<td>Interaction of sleep-related activity with normal tissue (near focus)</td>
</tr>
</tbody>
</table>

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which then inhibit the thalamocortical cells to membrane potentials where their intrinsic properties produce the delta oscillation (Steriade et al., 1991). Spindles and delta oscillations are mutually exclusive within a single thalamocortical neuron. Spindles are produced at relatively depolarized resting membrane potentials between −55 and −65 mV, whereas delta oscillations are seen at more hyperpolarized membrane potentials between −68 and −90 mV (Nunez et al., 1992).

In addition to the more easily observed sleep EEG oscillations, such as spindles and delta oscillations, the sleep EEG also shows a cortically generated slow oscillation at frequencies <1 Hz, typically 0.5 to 0.9 Hz. This activity is believed to be generated in the cerebral cortex. It survives in the cortex after thalamectomy (Steriade et al., 1993b) and is absent in the thalamus of decorticated animals (Timofeev and Steriade, 1996). It can even be reproduced in vitro in isolated cortical slices (Sanchez-Vives and McCormick, 2000). The slow oscillation consists of an excitatory and an inhibitory phase. During the excitatory phase, cortical neurons depolarize rapidly to reach a plateau lasting 0.5 to 1 seconds where they may fire action potentials. During the inhibitory phase, neurons hyperpolarize gradually. The reason for the switch between the excitatory and inhibitory phases is unknown but theorized mechanisms include reduced neurotransmitter release due to local depletion of [Ca2+]o (Massimini and Amzica, 2001) or due to activation of a slow Na+-dependent K+ current (Conte-ras et al., 2003). This oscillation shows widespread synchronization among different cortical areas via corticocortical connections (Amzica and Steriade, 1995; Contreras et al., 1996).

The slow oscillation is thought to form the basis for the K complex, which occur at periodic intervals in all stages of NREM sleep. K complexes are thought to represent fluctuating arousals and can be provoked by external sensory stimuli and intrinsic sleep oscillations. In addition, the slow oscillation when it projects to the RE cells of the thalamus is thought to trigger sleep spindles (Amzica and Steriade, 1997; Steriade et al., 1993a), such that sleep spindles are more common during the depolarizing phase of the slow oscillation. Recently, it has been reported that the slow oscillation may also group high-frequency oscillations (Le Van Quyen et al., 2010). The slow oscillation is underappreciated in clinical EEG for several reasons: (1) its frequency is often below that used for clinical recordings, to avoid artifacts such as movement and sweat and (2) its broad distribution makes it difficult to see in bipolar derivations.

A less obvious but interesting phenomenon related to NREM sleep is the so-called CAP [reviewed by Parrino et al. (2000)], which at this point is strictly defined based on EEG findings, the physiologic basis being unknown. NREM sleep can be subdivided into periods showing CAP and those not showing CAP (non-CAP). During CAP, there are alternating phases of periods containing arousal phenomenon lasting 8 to 15 seconds (phase A, or CAP-A) separated by slightly longer intervals, 15 to 20 seconds, of background activity without the arousal phenomenon (CAP-B). K complexes, sleep spindles, and arousals occur during CAP-A. Epileptiform discharges and seizures, both in primary generalized epilepsy and in focal epilepsy from the frontotemporal region, seem to occur predominantly during the CAP phase of NREM sleep and specifically during the CAP-A phase (Terzano et al., 1989). They are inhibited during CAP-B. However, in another epilepsy syndrome, benign epilepsy with centrotemporal spikes, there is no clear modulation of epileptiform discharges by CAP (Terzano et al., 1991).

INTERICTAL EPILEPTIFORM DISCHARGES AND SLEEP

The influence of sleep on interictal discharges in general can be summarized as follows: NREM sleep activates interictal discharges (both in number and in spatial extent) and REM sleep inhibits interictal discharges. However, the precise relationship is more nuanced and shows some variability depending on the type of epilepsy. For patients with primary generalized tonic–clonic seizures, interictal discharges are increased during NREM sleep, especially stages 1 and 2, and decreased during REM sleep (Declerck, 1986). Furthermore, generalized 3 to 4 Hz spike-and-slow-wave discharges occur in association with K complexes during stage 1 and 2 sleep. For patients with primary generalized myoclonic seizures, interictal discharges were more common at sleep onset and arousal from sleep than during waking. For absence epilepsy, sleep also activates the typical 3-Hz spike-wave discharge. The actual frequency of the spike-wave discharge also seems to change during sleep stages: highest during deeper stages (stages 3 and 4) of NREM sleep (Sato et al., 1973). Similarly, generalized spike-wave discharges associated with other forms of epilepsy also are increased in NREM sleep and decreased in REM, including the slow spike-wave discharge of Lennox–Gastaut syndrome (Degen and Degen, 1991) and the discharges of continuous spike-waves during slow-wave sleep (Nobili et al., 2001).

For partial onset seizures, early studies clearly demonstrated an activation of interictal discharges during sleep (Gibbs and Gibbs, 1947; Niedermeyer and Rocca, 1972), suggesting the importance of obtaining a sleep EEG tracing for diagnostic purposes. Most detailed studies have confirmed that NREM sleep activates interictal discharges in partial epilepsy and that REM sleep suppresses them (Frank, 1970; Malow et al., 1997, 1998; Rossi et al., 1984). In some studies, interictal discharges have been found to progressively increase with deeper stages of NREM sleep (Lieb et al., 1980; Malow et al., 1997, 1998; Sammaritano et al., 1991). However, others have found greater activation of interictal discharges during light NREM sleep, stages 1 and 2, not stages 3 and 4 (Ferrillo et al., 2000a; Montplaisir et al., 1982).

In addition to the variation in frequency of discharges, the spatial extent of the interictal discharges also seems to vary with sleep stages. Several reports have suggested that interictal discharges are more widespread during NREM sleep compared with waking and REM sleep (Adachi et al., 1998; Montplaisir et al., 1980, 1982; Sammaritano et al., 1991); in some cases, NREM sleep is associated with interictal discharges even from the contralateral hemisphere. Novel interictal epileptiform foci were seen in 53% of patients during NREM sleep (Sammaritano et al., 1991). Thus, discharges seen during NREM sleep may be less likely to reflect the true epileptic focus. As a result, the value of epileptiform discharges observed during REM sleep and/or waking may be higher than those during NREM sleep for localizing the true epileptic focus.

Even for West syndrome/infantile spasms, where the EEG characteristically shows the chaotic pattern known as hypsarrhythmia, there is an increase in background amplitude and an increased grouping/rythmicity of the spike-wave discharges during NREM sleep. During REM sleep, there is a decrease or even disappearance of this pattern during sleep (Hrachovy et al., 1981). The focal/multifocal discharges of Landau-Kleffner syndrome, or acquired epileptic aphasia, are also activated by non-REM sleep, becoming both more frequent and more widespread (Hirsch et al., 1990; Paquier et al., 1992).

In addition to interictal epileptiform discharges such as spikes and sharp waves, it has recently been shown that oscillations at high frequencies (typically >80 Hz) may be a hallmark of epileptic tissues. These high-frequency oscillations are sometimes further subdivided into ripples (roughly 80 to 200–250 Hz) and fast ripples (>200–250 Hz). The fast ripples seem to correlate better with pathophysiology, whereas ripples may be seen in nonepileptic tissue as well (Shouse et al., 2000). They are thought to be generated by...
local neuronal circuits within the neocortex or the hippocampus. It is not clear whether they reflect activity within the epileptic focus or, alternatively, synchronized activity in nearby tissue that may enable spread of epileptiform activity from the epileptic focus (Bragin et al., 2002; Schevon et al., 2009). In animal models, they have also been proposed to be important for the transition from interictal to ictal activity (Timofeev and Steriade, 2004). These have been recorded from patients with epilepsy using intracranial micro- and macroelectrodes and seem to correlate with the seizure-onset zone, in many situations better than the interictal discharges (Bragin et al., 1999; Jacobs et al., 2008, 2010). Similar to interictal spikes and sharp waves, such oscillation also seems to be increased with non-REM sleep (Bagshaw et al., 2009).

EPILEPTIC SEIZURES AND SLEEP

Early observations of the timing of seizures with respect to the sleep cycle concentrated on generalized tonic–clonic (or secondarily generalized) seizures in institutionalized patients (Gowers, 1885; Langdon-Down and Brain, 1929; Patry, 1931). They classified individual patients as having a seizure pattern that was diurnal (twice as many seizures during daytime as night, 42%–45%), nocturnal (twice as many seizures during nighttime as day, 19%–24%) or diffuse (33%–35%) [summarized by Patry (1931)]. Janz (1962) studied an outpatient population and classified epilepsies as being awakening (seizures immediately upon awakening or within a few hours or during relaxation after work, 34%), sleep (seizures during sleep, 45%), or diffuse (21%). He further studied detailed characteristics of these different groups [summarized in Mendez and Radtke (2001)]. These include that the awakening group was more likely to be cryptogenic (vs. symptomatic), hereditary, associated with petit mal seizures, and have a more benign course. At the other extreme was the diffuse group that was more likely to be symptomatic and have a poorer prognosis. He even recognized that among patients with seizures presumably related to a focal brain injury or brain tumor, there was a difference among different locations in the brain: frontal lobes lesions were commonly associated with sleep epilepsies: 58% for frontal lobe, versus 22% to 25% for temporal or parietal lobes.

In patients with primary generalized tonic–clonic seizures, the largest group of patients seem to have their seizures upon awakening (18%) or during the waking period (35%), 29% had seizures predominantly during sleep, and 18% were diffuse (Billard, 1982). In the case of absence of seizures, it is difficult to talk about clinical seizures during sleep because clinical manifestations are unlikely to be observed. However, as reviewed earlier, the epileptiform discharges do change during sleep.

For partial-onset seizures, likely due to heterogeneity in the location of onset (see below) and difficulty in ascertaining the precise number of seizures, especially at night, early attempts at classifying these patients in categories of awakening/waking, sleep or diffuse gave highly variable results [reviewed by Autret et al. (1999)]. More careful studies using long-term EEG recordings have shed some light on this topic, although conflicting data still remain. In general, it has been found that seizures originating in the frontal lobes are more likely to occur during sleep when compared with temporal lobe seizure. In one study, 61% of seizures in patients with frontal lobe epilepsy (FLE) occurred during sleep when compared with only 11% of patients with temporal lobe epilepsy (TLE) (Crespel et al., 1998). In this study, most nocturnal seizures occurred during stages 1 and 2; only 2 of 175 sleep seizures occurred during stage 3 or 4 and only 2 of the 175 in REM. In another study using similar techniques, frontal lobe seizures were found to be somewhat more likely to occur during sleep than temporal lobe seizures, 37% versus 26% (Bazil and Walczak, 1997). Seizures were most common during stages 1 and 2 of sleep, and least common during REM. Also, seizures in slow-wave sleep (stages 3 and 4) were significantly longer than those in waking or stage 2 (and possibly compared with those during REM sleep, although small numbers during REM sleep produced no statistically significant difference). Finally, seizures were much more likely to be secondarily generalized during sleep compared with waking, 35% versus 18%, a finding supported by other studies (Sinha et al., 2006). Interestingly, this difference was mainly due to the patients with TLE, 45% in sleep versus 19% in waking, and not the patients with FLE, 22% in sleep versus 20% in waking. An interesting case report demonstrating the possible effect of the seizure focus on the relationship between sleep and epilepsy is that of a patient with two independent foci for partial-onset seizures who kept an hour-by-hour seizure diary for >5 years (Quigg and Straume, 2000). This patient had episodes of confusion and orofacial automatisms originating from the right temporal lobe and episodes of abrupt left-hand pain originating from the right parietal lobe, both confirmed by intracranially recorded EEG. The right temporal lobe seizures were usually diurnal (peak at 12:10 PM) whereas the right parietal seizures were predominantly nocturnal (peak 2:50 AM). This demonstrates that even within a given patient, sleep can differentially affect seizure foci.

Some studies have suggested that arousal from sleep or the transition between sleep and waking may be what actually triggers seizures rather than the sleep state itself. This is distinct from the epilepsy syndromes that have been termed as awakening epilepsies, where seizures occur soon after waking (e.g., juvenile myoclonic epilepsy and epilepsy with generalized tonic–clonic seizures upon awakening). Awakening epilepsies tend to be primary generalized in nature. But even for seizures occurring during sleep, it has been observed that they occur during times of arousals or miniarousals, for example, during the CAP-A phase (Terzano et al., 1989). For seizures, it is difficult to assess if an arousal precedes a seizure or results from the seizure. For example, mesial temporal lobe seizures occurring during sleep have been suggested to be related to awakening (Wolf and Schmitt, 2002). However, intracranial recording suggest that arousal actually follows the onset of the seizure rather than preceding it (Malow et al., 2000).

Some studies have suggested that circadian rhythms can modulate seizure activity independent of the sleep–wake cycle. For example, rats that were made to have recurrent spontaneous epileptic seizures by electrically induced limbic status epilepticus have a similar fluctuation in timing of seizures with respect to the day–night cycle similar to the patients with mesial TLE (Quigg et al., 1998). This is despite the fact that, unlike humans, rats are nocturnal animals that sleep during the day light hours and are active at night. This suggests possible impact factors that are circadian but not directly related to sleep, such as activity within the suprachiasmatic nucleus, which is determined directly by the light/dark cycle independent of the sleep–wake cycle [reviewed by Quigg (2000)].

MECHANISMS FOR INTERACTIONS BETWEEN SLEEP AND EPILEPSY

There are several theories regarding how sleep could influence the abnormal hypersynchronization and hyperexcitability that are the hallmarks of epilepsy. One relatively straightforward idea is that fluctuations in the level of synchronization of cortical neurons during sleep and waking can promote or suppress the abnormal synchronization of the epileptic brain. For example, the increased synchronization during NREM sleep might make it easier for a hypersynchronized discharge to entrain a group of neurons, whereas when the neurons are relatively desynchronized, like during waking or REM sleep, it is more difficult to do so. The importance of neuronal synchronization during sleep for promoting epileptiform
activity is supported by studies in cats in which pharmacologic manipulations and lesions have been used to selectively produce REM sleep-like state without EEG desynchronization or REM sleep-like state without atonia (Shouse et al., 1989, 2000). Systemic application of the metabotropic acetylcholine receptor blocker atropine leads to a REM-like state (with atonia and the presence of REM-characteristic pontogeniculocipital waves) but with a synchronized EEG similar to NREM sleep including sleep spindles. These animals have increased interictal epileptiform discharges and electrographic seizures during this REM-like state, but without motor manifestations. However, lesions of the medial and lateral pontine tegmentum produce a REM-like state without atonia but with a desynchronized EEG. During this state, there is no increase in the number of interictal discharges or seizures; however, when seizures do occur, they are accompanied by motor manifestations because of the lack of atonia. These findings support the idea that it is the desynchronization of neuronal activity present during REM sleep that suppresses interictal and ictal discharges. By extension, the increased synchronization of neuronal activity during NREM sleep would be expected to enhance epileptiform activity.

There are several problems with neuronal synchronization being the primary role for explaining the interactions between sleep and epilepsy. First, although it is clear that there is increased synchronization during NREM compared with REM or waking, the amount and type of synchronized activity varies during NREM sleep. Activity in the delta frequency band (typical 0.5–4 Hz) has traditionally been used as a measure of the depth of NREM sleep—lowest in stage 1 and highest in stage 4. But other frequency bands, including the sigma band (12–16 Hz, correlating with spindle activity) and theta band (4–8 Hz) also show fluctuations during the course of sleep. As mentioned previously, although nearly all studies agree that non-REM sleep promotes interictal epileptiform discharges and REM sleep suppresses them, there is less clear agreement regarding what aspects of the activity during NREM are related to the interictal discharges. Some studies have suggested that the depth of sleep, i.e., progressing from stage 1 to 4, correlates with the number of interictal discharges (Clemens and Majaros, 1987; Malow et al., 1997, 1998; Sammaritano et al., 1991). The logarithm of the power in the delta frequency band (~0.5–4 Hz, log delta power) has been reported to correlate with frequency of interictal epileptiform discharges in partial-onset seizures (Malow et al., 1997, 1998). In these studies, the frequency of discharges also seemed to depend on the rate of increase in log delta power and, thus, was highest on the ascending limb of the rising phase of LDP, i.e., as the patient progressed through deeper stages of NREM sleep. Using similar techniques, however, another group has suggested that while in many patients interictal discharges do correlate best with log delta power, in other cases, they are better correlated with power in the sigma band or even in the theta band (Ferrilllo et al., 2000a, 2000b).

In these studies with a limited number of patients, there was no obvious clinical or EEG factor that seemed to predict which frequency band was the best predictor for epileptiform discharges for a particular patient (interictal discharges correlating with delta, sigma, or theta bands). One possibility is that sleep-related activity may not affect all parts of the brain equally. For example, sleep spindles tend to be best observed in the frontocentral regions. Thus, if they are critical to the effect of sleep on seizure, this effect would be expected to be greater in seizures coming from the frontocentral region. However, even among patients with FLE, there is significant variability in how sleep affects them. Another possible explanation is that some intrinsic property or characteristic of the epileptic focus determines which types of sleep-related activities will maximally activate it. The focus may have some intrinsic rhythmicity or oscillatory behavior; when a brain rhythm extrinsic to the focus has a similar frequency, a resonance type of phenomenon is created and the epileptiform discharges are boosted in the presence of this extrinsic brain rhythm. If the intrinsic rhythmicity is closer to the delta band, the discharges will correlate with LDP; however, if the intrinsic rhythmicity is closer to the sigma band, they will correlate more closely with sigma power or sleep spindles.

In trying to understand the relationship between sleep and epilepsy, it is important to keep in mind that most of our knowledge about sleep activity relates to the normal human or animal brain. How sleep activity is expressed within the abnormal brain and, specifically, within abnormal regions of the brain is largely unknown. The importance of the nature of the focal or generalized pathophysiology that is responsible for the epileptic seizures in relation to how sleep affects seizures has not been explored thoroughly. Its importance is hinted by the variability in the effect of sleep on seizures depending on epilepsy syndromes, location of seizure foci, and “severity” of the pathophysiology (i.e., idiopathic vs. symptomatic etiologies). There have been few investigations on the direct effect of sleep on individual neurons within the epileptic focus. Some studies have demonstrated that neuronal activity in the epileptic focus is modulated by sleep. For example, neuronal firing in the epileptic hippocampus is selectively enhanced by NREM sleep compared with the contralateral, nonepileptic hippocampus (Shouse et al., 2000). Furthermore, in a monkey model of epilepsy, individual neurons within an epileptic focus created by application of alumina cream showed increased firing rates during sleep (Mayanagi, 1977; Wyler et al., 1975). There seemed to be a difference in the modulation by sleep for lateral temporal versus mesial temporal foci: for lateral, interictal discharges were maximal during light sleep (approximately NREM stage 2) and for mesial, interictal discharges were maximal during deep sleep (approximately NREM stage 3) (Mayanagi, 1977). However, other studies have suggested that activity with the seizure focus may be relatively immune to modulation by sleep activity. For example, interictal discharges from the seizure focus seem to be less affected by the sleep–wake cycle than epileptiform discharges from other areas—specifically, they may persist in REM sleep whereas discharges from other areas are suppressed (Sammaritano et al., 1991). Presumably, the intrinsic abnormalities of the epileptic focus produce local hypereexcitability and hypersynchronization allowing for epileptiform activity even in the absence of extrinsic synchronizing mechanisms. However, for this epileptiform activity to spread to regions without significant intrinsic abnormalities, an extrinsic source of synchronization allows for easier propagation of the epileptiform activity. The synchronized activity that occurs during NREM sleep could provide this external source of synchronization. The lack of sleep-related modulation of activity within the epileptic focus may result from an alteration in the expression of sleep-related activity within the epileptic focus in some situations. The degree and nature of this alteration could vary with the type of focus. In extreme cases, sleep may not modulate the epileptic focus at all. This may explain why it is the patients with intractable and symptomatic epilepsies that show the most diffuse pattern of seizure activity with respect to the sleep–wake cycle (Janz, 1962). Even in these cases, sleep could still affect clinical seizures by effecting how easily they spread into nearby normal cortex, for example, to cause secondarily generalized seizures.

Some studies have suggested that rather than simply being a matter of increased synchronization, increased epileptiform activity and especially increased seizure activity during sleep may relate to arousals and sudden increases in excitability during sleep. For many types of seizures, the peak in seizure occurrence does not correlate with NREM sleep. Indeed many seizures associated with sleep actually correlate better with arousals or microarousals. These include seizures upon awakening, seizures that have been associated
with K complexes in autosomal-dominant nocturnal FLE (El Helou et al., 2008), and the occurrences of seizures during the active phase of the CAP-A. One possible explanation for the importance of arousals or microarousals is the enhanced excitation that occurs during these phenomena. This could be due to either the localized increase in cortical excitability due to the fluctuating cortical slow oscillation or the extrinsic excitation provided by glutamatergic and cholinergic projections associated with arousal/awakening. However, in other studies, it seems that the seizure onset may actually precede arousal (Malow et al., 2000). In this case, the arousal is thought to be a result of the seizure rather than a cause of it.

For generalized epileptiform discharges, the increased synchronized firing of neurons during NREM sleep is likely only a partial explanation for the increased occurrence of epileptiform discharges. It has been theorized that generalized epileptiform discharges and sleep oscillations such as spindles, K complexes, and delta oscillations share overlapping neuronal circuits and that epileptiform discharges may result from subtle changes in neuronal excitability or function that can corrupt normal sleep rhythms (or at least the circuits involved in their generation) into pathologic discharges [for review see the study by Beenhakker and Huguenard (2009)]. Similar to sleep spindles, generalized epileptiform discharges demonstrate cortical and thalamic activity that are time locked to each other. In addition, both spindles and spike-wave discharges can be generated in thalamic brain slice preparations (von Krosigk et al., 1993) by modulating the amount of GABAergic inhibition. Specifically, if GABA<sub>A</sub>-receptor-mediated inhibition is reduced, spindle-like oscillations are replaced by slower spike- and slow-wave types of discharges. Thus, it has been suggested that under conditions of increased excitability, sleep spindles can become or at least circuits involved in producing sleep spindles can produce spike- and slow-wave discharges. The fact that spike-wave discharges can occur in the waking animal suggests that it is more a matter of a common circuit producing both phenomenon rather than a sleep spindle being transformed into a spike-wave discharge.

One proposed mechanism for how the spindle-producing circuit could be triggered to produce spike-wave discharges is reduced inhibition among RE neurons. Collateral inhibition among RE neurons is thought to limit the degree of synchronization in the RE-thalamocortical neuron circuit (see Fig. 1). This limit could be overcome in several ways. One possibility would be decreased GABAergic transmission within the reticular neuron. Evidence supporting this hypothesis come from mice lacking the β3 subunit of the GABA<sub>A</sub> receptor, which is found at GABA<sub>A</sub>ergic synapses within the reticular nucleus but not at synapses between RE and thalamocortical neurons. In these animals, inhibition from collaterals within the reticular nucleus is effected while inhibition from RE to thalamocortical neurons is not. This leads to thalamic oscillations that are more synchronized and resemble epileptiform discharges (Huntsman et al., 1999). Another way to overcome the collateral inhibition among RE neurons is increased excitation of RE and/or thalamocortical neurons from the cortex, thalamocortical neurons, or ascending tracts (Bal et al., 2000; Blumenfeld and McCormick, 2000). The latter, increased input from ascending tracts, could explain the importance of arousals in triggering epileptiform discharges and seizures.

Increased excitation to RE neuron could also be responsible for altering the frequency of the oscillations from the ~10 Hz that is typical of sleep spindles to ~3 Hz that is more typical of spike-wave discharges. A theorized mechanism for this change is a change in the relative contribution of GABA<sub>A</sub> and GABA<sub>B</sub> receptors to the inhibitory synapse between RE and thalamocortical neurons. GABA<sub>A</sub>-mediated responses are much faster, leading to a quicker repolarization of the thalamocortical neurons and more frequent bursts of rebound action potentials. Conversely, GABA<sub>B</sub>-mediated responses are much slower and thus if they are main component of the IPSPs in the thalamocortical neurons, the bursts of rebound action potentials will be less frequent, leading to a slower oscillation when recorded from groups of neurons in the thalamus or the cortex. More intense stimuli will activate a larger proportion of GABA<sub>B</sub> receptors (located more peripherally at the synapse or even extrasynaptically), leading to a slower response. In fact, application of GABA<sub>B</sub> receptor antagonists caused the oscillation frequency to increase back to the spindle frequency range.

Even in some forms of focal epilepsy, abnormalities in the spindle-generating thalamocortical circuit may play a role. Scalp EEG and intracranial recordings from patients with autosomal-dominant nocturnal FLE have shown that nocturnal seizures may be preceded by abnormally prolonged spindles (Picard et al., 2007). Although the seizure itself may result from enhanced excitability due to the longer spindle, some abnormality in the spindle-generating circuit is likely to be responsible for the longer spindle in the first place.
Certain chemicals related to circadian rhythms and the sleep–wake cycle have also been proposed to play a role in the relationship between sleep and epilepsy. One of these is melatonin, although the precise effect of melatonin on neuronal excitability and seizures is unclear. Melatonin has been shown to possess anti-convulsant properties against seizures induced by electrical stimulation in rats (Mevissen and Ebert, 1998). In addition, removing the pineal gland in gerbils leads to seizure activity, which can be reduced by exogenously applied melatonin (Rudeen et al., 1980). These data would seem to conflict with the increased propensity for seizures during sleep in humans, because nighttime is when melatonin levels are highest. However, the data on melatonin levels in humans are conflicting, with some authors reporting increased levels and others reporting decreased levels [reviewed by Hofstra and de Weerd (2009)]. Similarly, some studies (mostly in children) have reported that exogenously applied melatonin can decrease seizure frequency; however, others have reported that melatonin can actually increase seizure frequency. Some of the conflicting results may be due the fact that seizures themselves may modulate melatonin levels, making it important to control for recent seizure activity when measuring melatonin levels (Bazil et al., 2000).

CONCLUSIONS

The relationship between sleep and epilepsy is obviously a complex one. For some forms of epilepsy, especially the primary generalized ones, the substrate for the interaction may include shared circuits that can be transformed under pathologic conditions to produce epileptic seizures. For focal and generalized epilepsies, the changes in synchronization of neuronal activity and neuronal excitability are likely to be critical in the relationship. However, the nature and degree of effect of these factors likely depends on the characteristics of the epileptic tissue itself—whether a focal lesion or a generalized disturbance of brain function. Like many areas of epilepsy research, much of the variability and conflicting data likely results from treating a heterogeneous condition such as epilepsy as a single (or even a small number of) entity (-ies). Although our understanding of sleep physiology and epilepsy pathophysiology has advanced significantly, there remain large areas that are unexplored or poorly understood.

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