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REVIEW ARTICLE

The Mutual Interaction Between Sleep and Epilepsy on the Neurobiological Basis and Therapy

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Abstract: ***Background*:** Sleep and epilepsy are mutually related in a complex, bidirectional manner. However, our understanding of this relationship remains unclear.

***Results*:** The literatures of the neurobiological basis of the interactions between sleep and epilepsy indicate that non rapid eye movement sleep and idiopathic generalized epilepsy share the same thalamocortical networks. Most of neurotransmitters and neuromodulators such as adenosine, melatonin, prostaglandin D_2, serotonin, and histamine are found to regulate the sleep-wake behavior and also considered to have antiepilepsy effects; antiepileptic drugs, in turn, also have effects on sleep. Furthermore, many drugs that regulate the sleep-wake cycle can also serve as potential antiseizure agents. The nonpharmacological management of epilepsy including ketogenic diet, epilepsy surgery, neurostimulation can also influence sleep.

***Conclusion*:** In this paper, we address the issues involved in these phenomena and also discuss the various therapies used to modify them.

Keywords: AEDs, CAP, EEG, epilepsy, NREM, REM, sleep.

1. INTRODUCTION

Epilepsy is a phenomenon of recurring seizures that affect many people around the world. It is a common neurological disorder characterized by the abnormal synchronization of neurons. This abnormality leads to seizures, the hallmarks of which are neuronal hyperexcitability and hypersynchrony of neuronal networks. One third of epileptic patients have seizures during sleep [1]. On the other hand, sleep disorders include insomnia, hypersomnias, circadian rhythm disorders, obstructive sleep apnea (OSA), and other sleep-related disorders. All of these are more common among epileptic patients, with prevalence estimates ranging from 24% to 55%. For example, insomnia is a common and important comorbidity in epilepsy; its severity adversely interacts with seizure control, and it has negative associations with quality of life [2]. Meanwhile, epilepsy affects sleep architecture, with qualitative and quantitative changes identified on polysomnographic studies in people with epilepsy [3, 4].

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The intimate relationship between epilepsy and sleep has long been recognized, but many aspects remain obscure. Therefore further studies are needed to clarify this relationship. In pursuit of this goal, we reviewed the neurobiological basis of the relationship between sleep and epilepsy as well as the relevant treatments.

2. THE NEUROBIOLOGICAL BASIS OF SLEEP AND EPILEPSY

2.1. Mechanisms Responsible for Sleep-Wake Regulation

Sleep, often described as the normal loss of consciousness, is a stage that reversibly disconnected with the environment, which means perceptual disengagement from and unresponsiveness to the sleeper's surroundings. Seemingly integrated, sleep in humans can be categorized into rapid eye movement (REM) and non-REM (NREM) sleep. Judging by the electroencephalogram (EEG), NREM sleep can be further divided into 3 stages: stage 1 (N1), stage 2 (N2), and stage 3 (N3) [5, 6]. REM sleep is defined by REM, the total absence of muscle tone, and the ability to dream vividly. Studies have shown that the generalized synchronous activity in NREM sleep can affect muscle tone and therefore facilitate the stereotypic movements that characterize the majority of epileptic seizures. Conversely, REM sleep during

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which the motor neurons are inhibited may block the movements associated with seizures.

Since seizures tend to occur during NREM sleep, the following discussion is mainly about the mechanisms underlying NREM sleep. It is now known that there are two opposite systems regulating vigilance states that is, the arousal system, which maintains arousal, and the sleep-promoting system, which initiates and maintains sleep. Although most neurons in the brain are less active during sleep than during wakefulness, the ventrolateral preoptic area (VLPO), located in the hypothalamus, remains active throughout the entire NREM sleep period [7]. A study conducted by Sherin *et al*. [8] using immunohistochemistry to determine the expression of c-Fos showed that the VLPO was specifically activated during sleep. Later, the same group [9], using both retrograde and anterograde tracing combined with immunohistochemistry, demonstrated that the VLPO sent gamma-aminobutyric acid (GABA)-ergic and galaninergic signals to all of the major nuclei that promote wakefulness, such as the tuberomammillary nucleus (TMN), dorsal and median raphe nuclei, and locus ceruleus (LC) [10, 11]. In addition, further studies revealed that the VLPO can also be inhibited by the arousal system [12, 13], pointing to the reciprocal relationship between the VLPO and sleep-wake regulation [11]. Likewise, the median preoptic nucleus (MnPO) also acts as a sleep promoter [14]. These two nuclei, interacting with the arousal system, form the "flip-flop" model proposed by Saper and his coworkers [15]. The suprachiasmatic nucleus (SCN), known as the pacemaker in mammalian brains, is involved in sleep-wake regulation as well. Several lines of evidence show that lesions of the SCN cause a redistribution of sleep bouts evenly within a 24-hour cycle [16-22] and can increase total sleep time [22, 23]. Other studies have shown that vasoactive intestinal peptide–positive GABA-ergic neurons in the core part of the SCN receive arousal-related serotonergic inputs from the midbrain raphe [24-26]. The SCN also projects to the subparaventricular zone (sPVZ) and then to the dorsomedial hypothalamus (DMH), which is strongly connected with neurons both in the VLPO and wake-prompting areas such as basal forebrain (BF), lateral hypothalamus (LH), posterior hypothalamus (PH), and brain stem [25, 27]. Thus, as suggested by Mistlberger *et al*. [19], the function of the SCN in sleep regulation is more to counter the effects of circadian phases than simply to prompt sleep or wakefulness.

Moreover, neuromodulators also participate in regulating the sleep-wake cycle. For example, adenosine, linking energy metabolism with neuronal activity and sleep, accumulates in the BF and cortex [28, 29] during prolonged wakefulness, and its nonselective antagonist caffeine prolongs wakefulness [30, 31]. The mechanism underlying this involves the activation of both adenosine A_1 and A_{2A} receptors (A_1Rs and A_{2A}Rs). Studies have shown that adenosine decreases neuronal activity and increases sleep by inhibiting wakefulness-promoting neurons [32, 33] and disinhibiting sleep-promoting neurons in the VLPO [34, 35]. Activation of A_1R in the BF, laterodorsal tegmentum (LDT), LH, and prefrontal cortex results in sleep [33, 36-38]. The infusion of selective A_{2A}R agonists to the subarachnoid space near the VLPO induced NREM sleep [39, 40] and increased the expression of c-Fos [41]. The homeostatic response after sleep deprivation was attenuated when the accumulation of extracellular adenosine was interfered [39]. Caffeine failed to induce wakefulness in the A_{2A}R knockout mice [42]. Later, the A_{2A}Rs in the shell part of nucleus accumbens were found to be essential for the arousal effect of caffeine [43]. Prostaglandin D_2 (PGD_2), the most abundant prostanoid in the brain, also participates in the regulation of sleep. The length of sleep rose after the infusion of PGD_2 into the third ventricle or preoptic area of rats [44] or the third ventricle of non-human primates [45] in a dose-dependent way; Sleep deprivation results in an increase in the concentration of PGD_2 in cerebrospinal fluid [46, 47]. PGD_2 is produced by either lipocalin-type PGD synthase (L-PGDS) or hematopoietic PGD synthase (H-PGDS) and interacts with the homeostasis system by linking with the DP_1 receptor (DP_1R) or chemoattractant receptor $CRTH_2$ (DP_2R) [48]. It is now well established that the system that regulates sleep is the L-PDGS/PGD_2/DP_1R system [40, 49, 50]. Melatonin is another intriguing example. Its production is ruled by the SCN, yet there is a feedback mechanism that allows melatonin to act as an internal synchronizer [51]. Other main neurotransmitters involving in the sleep-wake cycle are (a) noradrenalin, from neurons located in the LC, which plays a role in neural plasticity [52]; (b) serotonin, from neurons originating in the dorsal raphe, which can be activated by sensory information and stress [53]; (c) acetylcholine, which is abundant in both pontomesencephalic nuclei and the BF; (d) histamine, which lies in the TMN [54]; and (e) orexin/hypocretin, which is situated in LH and is important in the maintenance of wakefulness [55]. All the aforementioned waking nuclei secrete less neurotransmitter during NREM sleep, but unlike any other nuclei which secrete hardly any neurotransmitters during REM sleep [7], cholinergic neurons in the BF secrete normally, as during wakefulness [56]. Furthermore, sensory stimuli also promote wakefulness. The underlying circuit, also referred to the reticular activating system (RAS), is made up of thalamic relay neurons, thalamic reticular neurons, and cortex [7, 57]. The RAS not only serves as a switch between sleep and wakefulness [58, 59] but also generates slow-wave activity [60] and is responsible for gamma-band activity [61].

In brief, wakefulness, which involves a high level of cortical activity, is maintained by a complex and overlapping system involving in both circadian and homeostatic regulators, as described above. When the transition from wakefulness to sleep occurs, a chain of events is also initiated. Neurons in VLPO and MnPO are disinhibited when adenosine accumulates during wakefulness; thus, they send inhibitory signals to wake-promoting nuclei, leading to the onset of sleep [11, 27, 57, 62].

2.2. Microstructures Within Sleep and Their Relation to Epilepsy

With the developing of different EEG recording techniques and other methodologies, the microstructures hidden beneath sleep stages have now been revealed. Sleep spindles and κ-complexes are 2 particularly distinctive components of the N2 stage in humans [63]. The main function of κ-complexes is to protect sleep by suppressing cortical arousal

from external stimuli [64]. κ-complexes tend to be generated predominantly in the frontal parts of the brain [65] and then to be transferred to the thalamus, where sleep spindles ranging from 7 to 15 Hz and delta waves are produced [64, 66]. To be specific, sleep spindles originate from the reticular GABA-ergic neurons and are then transferred to the cortex *via* glutamatergic neurons, generating synchronous activities that can be seen on the EEG [59, 60, 67-70]. The N3 is characterized by slow waves and delta oscillations. The delta oscillations, ranging from 1 to 4 Hz, have both cortical [71] and thalamic [72] elements, although the thalamic level of their generation is better understood. At the thalamic level, the formation of delta oscillations, which seems to result from the same circuit that generates sleep spindles, actually utilizes the more hyperpolarized membrane potentials to initiate delta activity [63, 73]. Meanwhile the slow oscillations at frequencies below 1 Hz are generated exclusively in the cerebral cortex, which represents the synchronization of different cortical areas [74, 75]. The slow oscillations occur not only in N3 but also in other NREM sleep stages and thus function as connectors of the other EEG phenomena of NREM sleep [76, 77]. For instance, κ-complexes can be triggered by slow oscillations [78]. In fact, slow oscillations result from the "up" state, during which neurons are highly activated through depolarization, and the opposite "down" state, during which the cortical network is widely inhibited through hyperpolarization [57, 79, 80]. When it comes to estimating sleep intensity, slow oscillations and delta oscillations are often combined in slow-wave activity [81]. All the microstructures mentioned above actually reveal the interrelationships between cortical and thalamic structures within sleep [57]. In 1985, Terzano and his colleagues [82] found a periodic pattern within NREM sleep, representing the instability of sleep; this is described as a cyclic alternating pattern (CAP). During CAP, phases having more vigilance components are regarded as phase A, which alternates with the lower vigilance phase B [83]. This kind of alternation sheds light on the balance between sleep- and wake-promoting systems [57].

There is an intricate relationship between epilepsy and sleep [84, 85]. Like focal seizures [4, 86-88] and nocturnal frontal lobe epilepsy (NFLE), some seizures strike mainly during sleep [89-91] while others, as in the Landau-Kleffner syndrome, favor slow-wave sleep [57]. When seizures occur during the nocturnal period, in addition to a decrease in the duration of REM sleep and increase in REM sleep latency [4, 92, 93], sleep efficiency and total sleep time drop, causing sleep fragmentation [94]. Besides, seizures can also interfere with the microstructures of sleep (*e.g.*, CAPs and sleep spindles) [95, 96]. Moreover, several studies have shown that sleep deprivation acts as a trigger for seizures [97-103] by inducing NREM sleep afterwards and affecting cortical excitability [104]. Interictal spikes are abnormal discharges due to the incongruous synchronization of focal neuronal populations; they do not spread throughout the brain and thus cause no clinical symptoms [105, 106]. Recent studies focusing on generalized spike-wave discharges showed that they tended to occur during phase A of CAP and intensify with the progression of NREM sleep; they also altered morphologically during the latter sleep phase [104-106]. In conclusion, epilepsy and sleep may share the same neurophysiological mechanism, which is worth further investigating.

2.3. Mechanisms Responsible for the Interaction between Sleep and Epilepsy

Because NREM sleep represents a synchronization of brain activities [1, 107], studies of the relationship between NREM sleep and epilepsy are essential. When data on NREM sleep are combined with functional neuroimaging, neurophysiologic, and clinical data, it becomes clear that NREM sleep and idiopathic generalized epilepsy (IGE) share the same thalamocortical networks [57]. Thus a shift to or induction of NREM sleep would cause the expression of IGE. The same mechanism may also account for the correlation of sleep deprivation and seizures [101]. Spike-and-wave discharges (SWDs), characteristic of typical absence seizures at the EEG level, are seen in several types of IGE [57, 58]. Gloor *et al*. in 1978 raised the hypothesis that the same circuit generating sleep spindles might be responsible for SWDs, since SWDs seemed to favor light NREM sleep stages [108]. Several series of *in vivo* and *in vitro* experiments have verified this hypothesis [109-111], which involves, first, the inhibitory signal produced by thalamic reticular neurons on thalamic relay cells and, second, the complex thalamocortical circuitry built up with cortical pyramidal and thalamic relays as well as thalamic reticular neurons [57, 112]. However, SWDs and sleep spindles can also be interpreted by the different degrees of GABA-ergic inhibition in the thalamus [113]. In this hypothesized working mode, the synchronization of neurons in the reticular nucleus and thalamocortical network depends on the degree of GABA-ergic inhibition. Therefore reduced inhibition would allow an increase in the degree of synchronization, which would cause sleep spindles to transit to thalamic oscillations and facilitate epileptiform discharges. In some cases, seizures are actually related more to the instability of sleep than to increased synchronization because the onset stage of seizures appears during phase A of CAP [114-116].

Neuromodulators are also involved. Several studies showed that adenosine may contribute to the prevention of interictal spikes through the increased concentration of adenosine and the quantity of its receptors [117-120]. A recent study conducted by Kaushik and his colleagues [121] using different types of knockout mice demonstrated that PGD_2 produced by H-PGDS and acting on DP_1R was essential for seizure suppression and that the sleep after seizures strike was mediated by the same system responsible for physiological sleep. Melatonin is also involved in epilepsy. Bazil *et al*. found that the low baseline of melatonin increased remarkably after seizures in patients with intractable epilepsy [122]. Combined with other studies [123-125], these findings suggest that melatonin can relieve seizures either by improving sleep quality or through a more particular neuroprotective role. Other than adenosine and melatonin, serotonin and histamine, which promote wakefulness, are considered to have antiepilepsy effects [58]. However, orexin, which also promotes wakefulness, can induce seizures, and its level is increased in models of epilepsy as well as in patients [126].

Seizures also interact with circadian rhythms. Several lines of evidence using different animal models show that the light-dark cycle can alter the effects of seizures on sleep [127] and that c-Fos expression in SCN decreases after seizures [128]. In a recent study, Yi *et al*. [129] proposed the hypothesis suggesting that the central nucleus of the amygdala, lateral hypothalamic area, and SCN account for alterations in the period circadian clock 1 protein after seizures. In addition, the seizure threshold was reduced in an ARNT-like protein 1 (BMAL1) knockout mouse, suggesting a role for BMAL1 in the regulation of seizures [130].

3. SLEEP AND ANTICONVULSANT THERAPY

3.1. Effects of Antiepilepsy Drugs (AEDs) on Sleep

Because of the reciprocal relationship between sleep and epilepsy, it is not surprising that the treatment of epilepsy affects the sleep of patients with both generalized and partial epileptic seizures. Although the effects of AEDs on sleep architecture have been known for several decades, complications and the diversity of epileptic manifestations challenge us to clarify them. These effects may be different in partial and generalized seizure disorders, and they also vary according to the different mechanisms of action of AEDs.

In view of the pathogenesis of epilepsy, most AEDs on the market target neurotransmission by acting on the ion channels (Na^+, Ca^{2+}, Cl^-), GABA and glutamate receptors, or the process of release, inactivation, and reuptake of excitatory or inhibitory amino acids [131-134]. Generally, compared with conventional AEDs that tend to disrupt sleep, newer AEDs can improve it or have no effect on it. However, this conclusion is limited by small study samples and/or studies of short duration. The multitarget AED valproic acid (VPA) has been reported to consistently disrupt sleep and impair the attention of patients by increasing N1 sleep and decreasing slow-wave sleep (SWS) [135-137]. Carbamazepine (CBZ), which works as a blocker of the voltage-gated Na^+ channel, has been found to improve sleep continuity and increase SWS in healthy subjects [138]. Another study has also reported a significant increase in the percentage of SWS after treatment with CBZ in patients with epilepsy [139]. However, conflicting studies reported that CBZ did not influence the sleep of patients with epilepsy or disturbed it by increasing wake/sleep fragmentation, thus diminishing both SWS and REM sleep. Some researchers thought that these are merely initial effects that can be reversed by chronic treatment [135, 136, 140, 141]. A similar agent is phenytoin (PHT), an AED that falls into the same group as CBZ. PHT increased sleep latency and N1 sleep while also decreasing SWS and total sleep time [135, 136]. However, others claimed that patients treated with PHT showed a shorter sleep latency, decreased light sleep, and increased deep sleep [137, 142, 143]. In one study, this effect was also reported to be reversed with continuing therapy [143].

In contrast, newer AEDs, such as lamotrigine (LTG), have been reported to produce positive effects on the sleep of patients with epilepsy and to improve sleep stability [144, 145]. Another advantage is that LTG, like topiramate (TPM), does not impair patients' vigilance or cognitive function, nor does it cause daytime somnolence [144-147]. Zonisamide (ZNS), as a new AED or add-on therapy in focal epilepsy, has been reported to have no effect on nighttime sleep or to cause daytime somnolence [148]. These effects may be related to these drugs' multiple mechanisms of action, which influence both sleep and epilepsy. An exception was levetiracetam (LEV), a medication that binds to synaptic vesicle protein 2A. Its effect on sleep has been reported to be inconsistent. One study showed that LEV increased sleep efficiency without affecting sleep structure [139]; another demonstrated that it did not affect sleep time and efficiency during the night [149]. In more tests, however, LEV was reported to disrupt sleep, causing an increase in N2 sleep and a decrease in total sleep time, deep NREM sleep, and REM sleep [150, 151]. Most studies pointed to the possibility of daytime drowsiness [152].

Some AEDs are sedating agents in themselves and are also used as hypnotics or analgesics; these include the $GABA_A$ modulator phenobarbitone (PB) as well as the L-type Ca^{2+}-channel binding agents gabapentin (GBP) and pregabalin (PGN). They were expected to improve sleep in both healthy volunteers and patients by increasing SWS and REM sleep as well as reducing sleep latency, awakenings, and N1 sleep [136, 137, 142, 153-159]. Unlike the old AED PB which tends to cause daytime sleepiness as well as having negative effects on attention, psychomotor speed, mood, and cognition [137, 154, 158] PGN, which is newer, has been reported to improve attention in patients with partial epilepsy [156].

3.2. Drugs That Regulate the Sleep-Wake Cycle as Potential Antiseizure Agents

The beneficial effect of melatonin on sleep disorders has yet to be confirmed. Known as a sleep-wake-regulating drug for some types of insomnia and jet-lag syndrome [160], melatonin is also being considered as a potential antiepilepsy agent [161] since it could possibly modulate the electrical activity of neurons by influencing glutamatergic and GABAergic neurotransmission [160]. The anticonvulsant activity of melatonin had been observed in both animal models and patients, especially children and juveniles with intractable epilepsy [160, 162-165], producing not only a significant improvement of patients' sleep-related phenomena but also a reduction in seizure severity. Additional benefits have included improved physical, emotional, cognitive, and social function [160]. However, negative effects have also been noted, including EEG abnormalities in patents with temporal lobe epilepsy and increased seizure activity in neurologically disabled children [160]. After discussing 26 papers reporting an association between melatonin and epilepsy or seizures, a recent review suggests that in view of conflicting results from earlier work, more large-scale, double-blind, randomized, placebo-controlled clinical trials were needed [166].

Another agent is beprodon (BPD), an agonist of melatonin receptors [167, 168]. It is the first drug of this type to be evaluated for anticonvulsant and neuroprotective properties. There have been 2 reported phase II double-blind studies in patients with refractory focal epilepsy, but the results are not yet available [167].

Pitolisant, as an inverse agonist of the histamine H_3 receptor to block H_3 autoreceptors, is the first drug of this type used in clinics to treat refractory diurnal sleepiness in patients with narcolepsy, Parkinson's disease, or sleep obstructed by apnea/hypopnea [169, 170]. It has also recently been explored as an antiseizure drug medication. In one trial, after being given to 14 photosensitive adults showing generalized photoparoxysmal responses (4 of whom had myoclonic jerks), pitolisant significantly suppressed the subjects' generalized epileptiform discharges for 4 hours, with complete abolition in 6 patients [171].

There have been similar reports for other drugs. As a potent and long-lasting wake-promoting substance, modafinil is used in patients with excessive sleepiness for example, narcolepsy. This drug is remarkable for its low potential for dependence, abuse, and/or withdrawal symptoms [172]. Today this agent is also being investigated for its potential to exert antiepilepsy effects *via* adrenergic α_1 and histaminergic H_1 receptors [172]. In addition, magnolol, one of extracts and major bioactive constituents of *Magnolia dealbata*, is used in Chinese traditional medicine as a tranquilizer to treat epilepsy [173]. Its impact on sleep has recently been discovered, including a shortening of sleep latency and increases in the amounts of NREM and REM sleep [174]. Both of antiepilepsy and sleep-promoting effects are mediated by the $GABA_A$/benzodiazepine receptor complex, which offers us another insight into the close relationship between sleep and epilepsy [173, 174].

3.3. Nonpharmacological Management of Epilepsy

Despite the development of a growing number of AEDs serving as the primary treatment modalities, there are still about 20% to 40% of patients with newly diagnosed epilepsy who become refractory [175]. In contrast, nonpharmacological management of epilepsy sometimes has unexpected effects. These treatments can be divided into several categories, including the ketogenic diet and its modifications, epilepsy surgery, neurostimulation (vagus nerve stimulation, deep brain stimulation, responsive cortical neurostimulation, and transcranial magnetic stimulation) [176, 177].

3.3.1. The Ketogenic Diet and Its Modification

The classic ketogenic diet (KD), also called the long-chain triglyceride diet, includes a high ratio of fat (80%), adequate protein (15%), and low carbohydrates (5%). It has been used as a treatment for intractable childhood epilepsy since the 1920s [178]. Because of the restrictive role and diverse side effects of AEDs, the KD remerged in the late 20th century and came into more common use over the last 2 decades. Many studies in children with refractory seizures point to KD as a significant anticonvulsant alternative [179-181]. It has also been modified in terms of the ratio of fat components and the initiation of the diet with or without fast to facilitate its tolerability and expand its use. Such modifications include the medium-chain triglyceride diet, modified Atkins diet, low-glycemic-index treatment, and so on [178, 182].

Sleep structure during KD treatment was evaluated in 18 children with therapy-resistant epilepsy [183, 184], showing a significant decrease in total sleep, daytime sleep, and nighttime sleep and an increase in REM sleep. SWS remained intact. A correlation between increased REM sleep and quality of life was also found. However, another similar study reported partially conflicting results, finding a reduction in N2 sleep and REM sleep after 3 months of KD treatment [185].

3.3.2. Epilepsy Surgery

Surgery is an option for patients with medically intractable epilepsy. A careful evaluation should be performed to exclude nonepileptic events before the surgery [159]. Because recurrent seizures can harm the brain, early surgical intervention is now recommended for patients with well-defined focal seizures, especially for children with focal epilepsies and adults with temporal lobe epilepsy [176]. While moderating or eliminating the manifestations of seizures, successful epilepsy surgery can also improve sleep quality, sleep architecture, and obstructive sleep apnea with reducing excessive day time sleepiness in patients with focal epilepsy [161]. Improvements in sleep architecture (such as increased total sleep and REM sleep) caused by surgical treatment may be related to a reduction in the number of seizures and interictal epileptiform abnormalities [186]. Using questionnaires (Epworth Sleepiness Scale [ESS] and Pittsburgh Sleep Quality Index, [PSQI]) to assess daytime sleepiness and sleep quality, one study found that surgery significantly improved subjective sleep conditions in patients with partial recurrent seizures of temporal origin. This effect was not correlated with gender, AED class, age, or seizure frequency [187].

3.3.3. Neurostimulation

Neurostimulation is always the third line of adjunctive antiepilepsy treatment for patients with refractory partial epilepsy; it has been shown to influence a pathological substrate and to achieve a therapeutic effect by sending electrical or magnetic pulses to brain and nerve tissues directly or indirectly [176, 188, 189].

3.3.3.1. Vagus Nerve Stimulation

VNS is the oldest and most frequently used neurostimulatory modality [188, 189]. It was approved in Europe in 1994 and in the United States in 1997 [168, 177]. A stimulator that can send electrical impulses to the vagus nerve is implanted in the left cervical region. Besides its antiepilepsy effects [190, 191], the influence of VNS on sleep has also been studied in many other experiments. It has been reported that VNS at low stimulus intensities can reduce daytime sleepiness and promote daytime vigilance in patients with epilepsy and that it therefore can have a positive effect on their quality of life [192, 193]. In nighttime sleep, VNS in children induced a significant increase in SWS and a decrease in sleep latency and N1 sleep [194]. In spite of these positive effects, many negative respiratory effects were also noted, such as hoarseness, dyspnea, and laryngeal irritation due to autonomic nervous system dysfunction [195]. According to some studies, it was common for this modality to affect respiration during sleep and even to cause a severe nocturnal OSA or respiratory sinus arrhythmia, especially in children or patients with preexisting OSA [195-199]. In turn, it also altered patients' brain function for the worse. A trial

of continuous positive airway pressure might resolve this issue [196].

3.3.3.2. Deep Brain Stimulation (DBS)

DBS is an intracranial technique that places electrodes stereotactically into specific nuclei or regions of the brain and sends electrical stimuli directly to crucial brain structures or epileptogenic foci [186]. It is a mainstream therapy for several movement disorders and neuropsychiatric conditions, and today DBS is playing an increasing role in refractory epilepsy [200]. Various neural targets have been investigated in numerous clinical and animal studies involving the cerebellum, brain stem, reticular activating system, hypothalamus, thalamic basal ganglia, basal forebrain, limbic system, and so on. The feasibility, benefits, and pitfalls of such therapy vary with the targets of DBS [201-204]. One study reported that epilepsy patients undergoing DBS directed to the anterior nuclear thalami experienced significantly more electroclinical arousals during the stimulation periods. Moreover, the number of arousals correlated positively with the level of DBS voltage [205].

3.3.3.3. Responsive Cortical Neurostimulation and Transcranial Magnetic Stimulation

Unlike the classic VNS and DBS systems, which are open-loop systems (stimulation independent of seizure activity), RNS is a closed-loop system, which means that the electrical stimulus is delivered directly to the seizure focus in response to seizure activity [176, 200]. The U.S. Food and Drug Administration has recently approved it as a treatment for epilepsy that is resistant to medical intervention [177].

As a noninvasive brain stimulation technique, TMS is relatively inexpensive and safe. Targets vary from cerebellum, thalamus, and basal ganglia to vagal nerve and epileptogenic focus. The antiepilepsy effect of TMS has been approved in some studies [206, 207], but current research is insufficient to establish TMS as a treatment modality for epilepsy [161].

As to the treatment of disordered sleep, thus far there are no data regarding the influence of RNS and TMS on sleep in patients with epilepsy.

CONCLUSION

Although current studies have confirmed a strong relationship between sleep and epilepsy, the roles of both require further elucidation, in particular to clarify the psychiatric consequences of these disorders and their treatment.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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