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REVIEW

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The interaction between circadian rhythm and epilepsy

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Abstract

Evidence about the interaction between circadian rhythms (CR) and epilepsy has been expanded with the application of advanced detection technology. An adequate understanding of how circadian system and epilepsy interact with each other could contribute to more accurate seizure prediction as well as rapid development of potential treatment timed to specific phases of CR. In this review, we present the reciprocal relationship between CR and epileptic activities from aspects of sleep effect, genetic modulation and brain biochemistry. It has been found that sleep-wake patterns, circadian timing systems and multidien rhythms have essential roles in seizure activities and interictal epileptiform discharge (IED). For instance, specific distribution patterns of seizures and IED have been reported, i.e., lighter non-rapid eye movement (NREM) sleep stage (stage 2) induces seizures while deeper NREM sleep stage (stage 3) activates IEDs. Furthermore, the epilepsy type, seizure type and seizure onset zone can significantly affect the rhythms of seizure occurrence. Apart from the common seizure types, several specific epilepsy syndromes also have a close correlation with sleep-wakefulness patterns. Sleep influences the epilepsy rhythm, and conversely, epilepsy alters the sleep rhythm through multiple pathways. Clock genes accompanied by two feedback loops of regulation have an important role in cortical excitability and seizure occurrence, which may be involved in the mTORopathy. The suprachiasmatic nuclei (SCN) has a rhythm of melatonin and cortisol secretion under the circadian pattern, and then these hormones can feed back into a central oscillator to affect the SCN-dependent rhythms, leading to variable but prominent influence on epilepsy. Furthermore, we discuss the precise predictive algorithms and chronotherapy strategies based on different temporal patterns of seizure occurrence for patients with epilepsy, which may offer a valuable indication for non-invasive closed-loop treatment system. Optimization of the time and dose of antiseizure medications, and resynchronization of disturbed CR (by hormone therapy, light exposure, ketogenic diet, novel small molecules) would be beneficial for epileptic patients in the future. Before formal clinical practice, future large-scale studies are urgently needed to assist prediction and treatment of circadian seizure activities and address unsolved restrictions.

Keywords: Epilepsy, Circadian rhythm, Sleep, Mechanisms, Chronotherapy

Background

Circadian rhythm (CR), one of the most basic rhythms in mammalian behavioural and physiological processes, has been studied for hundred years. Under the 24-h day-night cycle, endogenous biological rhythms are generated by a central pacemaker of the suprachiasmatic nuclei (SCN) in the hypothalamus and control various organ systems through numerous neuronal connections and hormonal factors [1–3]. Emerging evidence suggests that the disrupted CR leads to multiple diseases such as cancer, mood disorder, and neurogenerative diseases [4–6]. Epilepsy is one of the most common neurological disorders characterized by spontaneous and recurrent seizures [7], with 30–40% of patients remaining refractory to current antiseizure medications (ASMs) [8]. Thus, alternative

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or adjunctive treatments are urgently required. CR and epilepsy have a crosstalk in several physiological processes such as sleep-wakefulness cycle, expression of clock-related genes, hormone secretion and epileptic activities [9–12]. A better understanding of the interaction between CR and epilepsy could facilitate more accurate prediction and potential therapeutic strategies. In this review, we will describe the reciprocal relationship between CR and epilepsy from several aspects including the sleep effect, genetic modulation and brain biochemistry, and then discuss accurate prediction algorithms and therapeutic strategies based on the chronoepileptology of patients with epilepsy.

Sleep pattern and epilepsy

Effects of sleep on epilepsy

CR modulates the brain function in several aspects, of which the regulation of sleep-wakefulness rhythm is the most important due to the different brain excitation-inhibition balances during sleep and wakefulness phases [13, 14]. A study has shown that 42% of seizures are diurnal, 21% are nocturnal and the remaining 37% are of the mixed type, indicating a significant difference in baseline seizure amount between the sleep and wakefulness phases [15]. Nearly half of the seizures occur preferentially at sleep [16] and the majority of seizures in sleep tend to begin during non-rapid eye movement sleep (NREM) [17]. In addition, a study investigating the seizure frequency in various sleep stages in patients with epilepsy showed that seizures occurred frequently at NREM sleep stage 2, followed by stage 1 and then stage 4 and stage 3 (61% in stage 2, 20% in stage 1, 14% in stage 4 and stage 3) [18]. With the advent of long-term video electroencephalography (EEG) recording of epileptiform activity, distribution of interictal epileptiform discharges (IEDs) in longer periods of time has been revealed [19, 20]. The IEDs tend to be activated during NREM sleep stage 3 and relatively inhibited during REM sleep in patients with epilepsy [21]. A comprehensive meta-analysis showed that the IED incidence is 2.46 times higher in NREM sleep stage 3, 1.75 times higher in stage 1 and 1.69 times higher in stage 2 than in REM sleep [22]. However, IEDs during REM sleep stage are more accurate for seizure localization while IEDs that occur during NREM sleep stage are likely to be widespread [23]. There is a specific distribution pattern of seizure and IED, with lighter NREM sleep (stage 2) inducing seizures while deeper NREM sleep (stage 3) activating IEDs. Interestingly, these two stages both have spindle waves in EEG recording. The frequent activation of IED or seizure during NREM sleep may be attributed to neurotransmitter change and progressive neural synchronization [18]. The gamma-aminobutyric acid (GABA) regulation decreases with the gradual reduction of the acetylcholine (Ach) level, which deactivates the suppressive GABAergic neurons of the reticular nuclei, mediating hyperpolarization of the excitatory thalamocortical network [24], and hypersynchronization during NREM sleep facilitates thalamocortical spindle wave to transform into spike wave [25]. On the contrary, the REM sleep stage characterized by suppression of the thalamocortical synchronization inhibits the spread of epileptiform discharge [26]. Similar effects on the thalamocortical circuitry have also been demonstrated for other monoamine neurotransmitters [27]. In addition, under normal conditions, concurrent drop of adenosine level and increase of adenosine kinase at the transition from wakefulness to sleep have been described, which may lead to lowering of seizure threshold in lighter NREM sleep stage and also be involved in transition of sleep stages and sleep arousal, therefore affecting seizure distribution [28]. In addition, adenosine exhibits an anticonvulsant effect while adenosine kinase shows a reverse effect [29].

In a study, epileptiform discharges were shown in 52% of patients during EEG after sleep deprivation, independent of sleep depth [30]. Therefore, in terms of EEG monitoring, sleep deprivation can be considered as a common firing method to induce epileptiform activity. Clinically, sleep deprivation after the morning also increases the seizure probability [14]. Arousal from sleep would lead to transition into lighter sleep stage and then back to deeper sleep stage, and seizures tend to occur on this descent back to deeper sleep [9]. Recently, in a longitudinal EEG investigation, sleeping longer by 1.66 ± 0.52 h, may offer protective effects in patients with refractory focal epilepsy, reducing the seizure odds by 27% in the following 48 h [31]. Cyclical alternating patterns, characterized by more sleep fragmentation, are more likely to promote seizures in sleep [32].

Frontal lobe seizures (FLS) tend to occur during sleep compared to temporal lobe seizures (TLS) [33]. For instance, 61% of FLS occur during sleep compared to only 11% of TLS based on a study of 30 patients receiving 5 days of continuous video-EEG monitoring. In addition, 22% of FLS have secondary generalization seizures during sleep compared to 20% during wakefulness, whereas TLS secondary generalization occurs at a rate of 35% during sleep and 18% during wakefulness [34]. It has been indicated that FLS occur more often during sleep than TLS; however, compared with FLS, TLS tend to undergo secondary generalization seizures when occurring during sleep [9]. In addition, seizures are more likely to occur frequently during sleep independent of day-night cycles for FLS. Sleep, especially NREM sleep, is the most robust predictor for seizure occurrence in lesional or genetic form of epilepsy, regardless of the

location of ictal-seizure onset zone [35]. In contrast, a majority of TLS tend to occur following the clock phase of CR, independent of the vigilance state [14]. As shown in several studies, TLS have a higher seizure frequency in the light than the dark phase in both animals and humans [36, 37]. The seizure-like discharges displayed two peaks during the light and dark phases, respectively, in an atypical absence epilepsy model [38]. Generalized tonic-clonic seizures reached one peak during the dark phase in Aldh5a1−/− mice model [39]. Contrary to these results, evidence suggests that slow-wave sleep and passive wakefulness seemed to promote the occurrence of spike-wave discharge (SWD) in a WAG/Rij rat model, regardless of the environment condition (light) [40]. This discrepancy may be explained by the uncoupling of SWD and motor rhythm during light conditions, because the sleep-wakefulness rhythm, considered to be governed by a weaker oscillator, loses its organization earlier than the more robust oscillator of motor rhythm [40]. Another potential explanation is the differences in animal models, seizure onset zones and epilepsy types between these studies [41]. With the clinical application of closed-loop implanted neurostimulator system, a longer-period monitoring of neuronal activity has become possible. In a study of 37 drug-intractable epileptic patients implanted with a closed-loop system, IED activities were found with a multidien period of length (commonly 20–30 days), and the multidien periodicities were stable for up to 10 years [42]. Similarly, another study also reported multidien periods of seizures and IEDs (6 days and 5–7 days, respectively) [43]. Therefore, sleep-wake cycles, circadian clock systems, and multidien rhythms have essential roles in seizure occurrence and IED activities [14].

Moreover, epilepsy type, seizure type, and seizure onset zone can affect the rhythm of seizure occurrences [44, 45]. In patients with idiopathic generalized epilepsy, tonic-clonic and tonic seizures occur predominantly during sleep, whereas other generalized seizures, such as myoclonic, clonic, atonic and absence types, occur mostly during wakefulness [46]. There are close connections between seizure onset zone and seizure rhythms in focal epilepsy. In focal epileptic patients with seizures originating from the frontal lobe, most of their seizures occur at night (4:00–7:00 a.m.) while the occipital seizures and temporal seizures reach a peak in the afternoon (16:00–19:00 and 13:00–16:00, respectively) [47]. A mainly bimodal distribution of seizures has been shown in mesial temporal lobe epilepsy, with peak frequencies in the early morning and the late afternoon [48, 49]. Currently, the parietal seizures have not shown a definite pattern possibly due to the anatomical ambiguity [41]. The parietal lobe is subdivided into the fronto-parietal and occipito-parietal regions on the basis of combination with adjacent areas [50]. Of note, the occurrence of frontal lobe seizures is 12-h out of phase with occipital lobe seizures, with the frontal lobe seizure reaching a trough, while the occipital lobe seizure occurrence being at a peak between 16:00 and 19:00 [47]. In conclusion, further studies are needed to determine whether all these results could be applied to predict the seizure occurrence for epileptic patients in clinical practice.

Sleep-related epilepsy syndromes

In addition to sleep-wake patterns affecting common epilepsy types, several specific epilepsy syndromes also show a tendency of correlation with sleep. One of the most common idiopathic generalized epilepsy syndromes, juvenile myoclonic epilepsy (JME), tends to occur on the transition from sleep to wakefulness in the early morning. In patients with idiopathic focal epilepsy syndromes, benign epilepsy with centrotemporal spikes (BECTs), autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), Landau-Kleffner syndrome (LKS) and epilepsy of childhood with occipital paroxysms (BECOP) and electrical status epileptitus during slow wave sleep (ESES) also have a well-documented relationship with sleep [51, 52].

JME, characterized by recurrent myoclonic jerk shortly after awaking in the early morning, is extremely susceptive to sleep deprivation. A potential explanation of higher seizure susceptibility at this time of the day is that, using transcranial magnetic stimulation, increased cortical excitability occurs in JME patients during the early morning compared with focal epilepsy patients or healthy control subjects [53]. Sometimes the myoclonic jerk is slight and even ignored because of its presentation as a simple clumsiness; furthermore, generalized tonic-clonic seizures could begin independently or precede the myoclonic jerk [52, 54]. In addition, patients with JME favor the evening chronotype and often suffer cognitive impairment possibly as an early awakening during the morning [12].

Accompanied by the secondary generalization with characteristic central and temporal spikes unilaterally or bilaterally in the EEG, BECT has a typical presentation with paresthesia or clonic or tonic activity of the face, tongue and throat [55]. The centrotemporal discharges become more frequent with higher amplitude during NREM sleep compared to the wakefulness. The progress of BECT is generally benign with an excellent response to medicine and remission in adolescence [9]. However, BECT patients may degenerate into epileptic encephalopathy in the form of ESEC and often suffer memory and cognitive dysfunction [56]. Impaired cognitive function may lead to increased nocturnal discharge that is involved in the plastic function that refreshes synapses

during sleep [57]. However, it has been found that lowering the nocturnal discharge rate is still beneficial for improving cognitive function, despite the possible side effects of anti-IEDs medication (e.g., diazepam) [58].

ADNFLE is a type of idiopathic focal epilepsy that is identified with a genetic basis, with clusters of complex and stereotyped hypermotor seizures in the frontal lobe during NREM [59]. It is similar in clinical and neurophysiological manifestations with sporadic nocturnal frontal lobe epilepsy, frequently accompanied by paroxysmal dystonia, sudden arousal and nocturnal wandering [9]. In addition, over half of the patients have normal in interictal EEG during sleep and only a few patients display a clear-cut epileptic activity in ictal EEG recordings. ADNFLE diagnosis is difficult in clinical practice because the nocturnal manifestation of symptoms resembles other sleep disorders [60]. About 10–15% (approximately 12%) of the ADNFLE families carry mutational genes that code for subunits of the neuronal ACh receptor (nAChR) [59]. The nAChR is a pentameric ion channel permeable to cations such as Ca^{2+}, and can result in membrane depolarization and then induce post-synaptic excitation or stimulate neurotransmitter release upon activation by ACh [61]. The dysfunction of inhibitory and excitatory transmitters mediated by mutation of the nAChR gene may trigger frequent seizures. The sleep-wake cycle is regulated by inhibitory and excitatory transmitters in several brain regions such as the locus coeruleus, the intralaminar nucleus of thalamus, the basal forebrain and the neocortex. In particular, the cholinergic projections into the thalamus nuclei are related with the regulation of thalamocortical oscillations occurring during sleep. Impairment of the function of AChRs interferes with the sleep-wake cycle and provokes seizures, thus explaining why seizures occur prevalently during sleep [60]. Moreover, emerging evidence suggests that nAChRs are a promising therapeutic target for ADNFLE patients and some typical ASMs can regulate the neurotransmitter-gated ion channel mediated by AChRs [59]. Further studies are still needed to validate these findings.

LKS is a type of acquired epileptic aphasia with language regression and epileptiform activity in children aged between 3 and 9 years [62]. LKS often occurs with continuous local spikes during sleep and also atypical spike waves in the temporal regions bilaterally [9, 63]. Moreover, the epileptiform activity is associated with deterioration of language acquisition and persistent neuropsychological deficits [57, 64]. In patients with LKS, early administration of steroids or adrenocorticotropic hormone (ACTH) can alleviate symptoms and normalize EEG [65]. BECOP is a type of idiopathic localization-related epilepsy in children and is characterized by various visual symptoms, convulsive phenomena and autonomic instability during the sleep. EEG recording of BECOP shows unilateral or bilateral spike-wave complexes over the occipital regions in sleep, which are, however, suppressed by the wakefulness [66].

Effect of epilepsy on sleep

Sleep influences the epilepsy rhythm, and epilepsy in turn alters the sleep rhythm. Epilepsy per se, seizure and interictal epileptiform activity would disrupt sleep including sleep quantity, sleep quality and sleep architecture [67]. Emerging evidence suggests that the sleep architecture is often altered in patients with epilepsy, including reduction of total sleep time and REM sleep, and increase of arousal and stage shifts, especially for those whose seizures are poorly controlled [68]. Furthermore, the occurrence of a seizure may disrupt sleep patterns by elongating sleep and, if the seizure occurs during sleep, reducing the quality of sleep [31]. In a study in 2017, the REM percentage and sleep efficiency were decreased, the total arousal index was increased, and the REM latency was prolonged in patients with epilepsy, compared with the healthy controls [69]. In a study comparing the effect of seizures occurring at night or day on sleep architecture, the REM sleep time was reduced from 18 to 12% by the seizures in the daytime and from 16 to 7% by seizures at night [70]. In addition, in seizure-free night, sleep is disintegrated more often in patients with epilepsy than in non-epilepsy subjects. These results may be attributed to the disruption of sleep and restraint of normal sleep progression by IED [71]. Regarding the effect of seizure type, patients with generalized seizures tend to suffer sleep abnormalities compared to those with simple or complex partial seizures [9]. Patients who become seizure-free following epilepsy surgery or ASM administration have a normalized sleep architecture and an improved sleep quality [72, 73]. There are two potential mechanisms mediating the disrupted sleep architecture in epilepsy. First, reticular nucleus of the thalamus (RNT) is involved in triggering of wakefulness [74]. A study has found that sleep disruption is associated with decreased excitability of RNT interneurons possibly due to the declined rebound firing after hyperpolarization, leading to sleep impairment [75]. The second mechanism of disturbed sleep is the dysfunction of hypothalamus in epilepsy. Spontaneous epileptic rats show neuronal loss in the dorsomedial hypothalamus, an important region for normal sleep regulation. Thus, hypothalamic pathology may be a link between epileptiform activity and altered sleep architecture [76].

Epileptic patients have a higher prevalence of comorbid sleep disorders than healthy controls, and patients with current seizures suffer more sleep disorders than these seizure-free epileptic patients. These sleep disorders

are more likely to lead to sleep deprivation, sleep fragmentation and hypoxia, therefore, reducing the seizure threshold and promoting epileptogenesis [77]. On the contrary, multiple factors can result in breathing abnormalities during seizures. For instance, seizures spread from local brain lobes to the brainstem respiratory center and eventually cause central sleep apnea [9]. These possibilities may also lead to sudden unexpected death in the epilepsy population. ASMs are still the most potent first-line treatment for epileptic patients and ASMs exhibit both beneficial and harmful effects on sleep independent of their antiseizure effect. Phenytoin may disrupt sleep, whereas carbamazepine and newer-generation ASMs (lamotrigine, pregabalin and gabapentin) appear to consolidate sleep in a variety of common conditions [78]. In brief, sleep disruption may be related to epilepsy per se, seizure activity, comorbid sleep disorders and the effect of antiseizure medication in epileptic patients, which in turn result in poor seizure control. Apart from effects on sleep-wake patterns, epilepsy also has adverse effects on other circadian activities, including temperature rhythm and rest-activity period [49, 79]. A better understanding of the mechanisms underlying sleep and CR disruptions can help epileptic patients with sleep disorder and CR disturbance.

Clock genes and epilepsy

To our knowledge, the imbalance of inhibitory and excitatory neurotransmitters is a currently recognized mechanism of epileptogenesis and the expression of numerous ion channels and neurotransmitter receptors is modulated by the circadian rhythms [14]. With exposure to a 24-h light/dark cycle, every single cell exhibits a genetically programmed rhythm, coordinated by the SCN involved in positive and negative feedback loops of clock-related gene transcription and translation [80, 81]. By serving as transcriptional activators, clock-related genes have rapid responses to the environment condition, which influences the phase of clock to modulate the daily rhythms of behavior and physiology [82]. There are two vital genes for the generation of the circadian clock in the SCN cells, including circadian locomotor output cycles (Clock) gene (a clock circadian regulator) and arylhydrocarbon receptor nuclear translocator-like (Bmal1) gene. Transcripts of these genes are translated and the proteins form the CLOCK/BMAL1 heterodimeric complex in the cytoplasm [80]. The CLOCK/BMAL1 complex translocates to the nucleus, where it binds to specific E-box motifs and then drives the transcription of target genes including Cryptochrome (Cry1, Cry2) and Period (Per1, Per2, Per3) and other downstream genes (TEF, DBP, HLE) [14]. mRNAs of Pers and Crys are then translated into PERs and CRYs proteins in the cytoplasm. Upon increase of levels, PERs and CRYs dimerize and translocate into the nucleus where they reduce the transcriptional activity of the CLOCK/BMAL1 complex, further restraining their own transcription (Fig. 1). This negative feedback loop is also indirectly supported by the phenomenon that the Crys and Pers reach their peaks of expression during the day, whereas the transcription of Bmal1 reaches its peak at midnight (anti-phase to Crys and Pers expression) [83]. This feedback loop along with others is crucial to the generation of endogenous rhythms for adaption to the diurnal-nocturnal cycle.

The clock-related genes not only affect the CR, but also modulate the epileptic susceptibility [84]. In a mouse model with deletion of three PAR bZIP (proline and acidic amino acid-rich basic leucine zipper) transcription factors, the audiogenic seizure threshold is decreased and spontaneous seizures occur with a circadian trend similar to the circadian distribution of sleep [85]. These data provide evidence that the downstream clock-related genes are associated with seizure susceptibility. Further study by Gerstner et al. supported for the first time the direct relationship between Baml1 gene and circadian epileptic activities in an animal model of electrical stimulation-induced seizure [11]. In their study, deletion of Baml1 gene not only abolished the circadian profile of seizure susceptibility in the mice, but also significantly reduced the seizure threshold compared to the wild-type mice. Regarding the Clock gene, its protein product, which is a core component of the CLOCK/BMAL1 complex, plays an important role in epileptonenesis. A study based on targeted deletions of the Clock gene in excitatory neurons in mice showed a lowered seizure threshold and sleep-related seizure occurrence, independent of SCN regulation of the sleep/wake cycle as Clock was preserved in SCN [86]. Interestingly, mice with deletion of Clock gene have decreased dendritic spine formation and altered electrophysiological hallmarks of neuronal microcircuits. These results supported that the loss of function of clock-related genes may disrupt the balance between neuronal excitability and inhibition, leading to the occurrence of seizures [87, 88]. On the other hand, some studies have also found disturbed expression of clock-related genes in epilepsy [79, 89]. The expression of Clock, Baml1 and Cry2 is decreased in both the early post-status epileptic (SE) phase and the epileptic phase, while the expression of Cry1 and Per1 is increased in the early post-SE phase and then decreased to the baseline level in the epileptic phase compared to the control condition [89]. In the epileptic Kcna1-null mice, in addition to disrupted diurnal and circadian rest-activity patterns, oscillations of several clock-related genes including Clock, Bmal1, Per1, and Per2 are also attenuated in the anterior hypothalamus

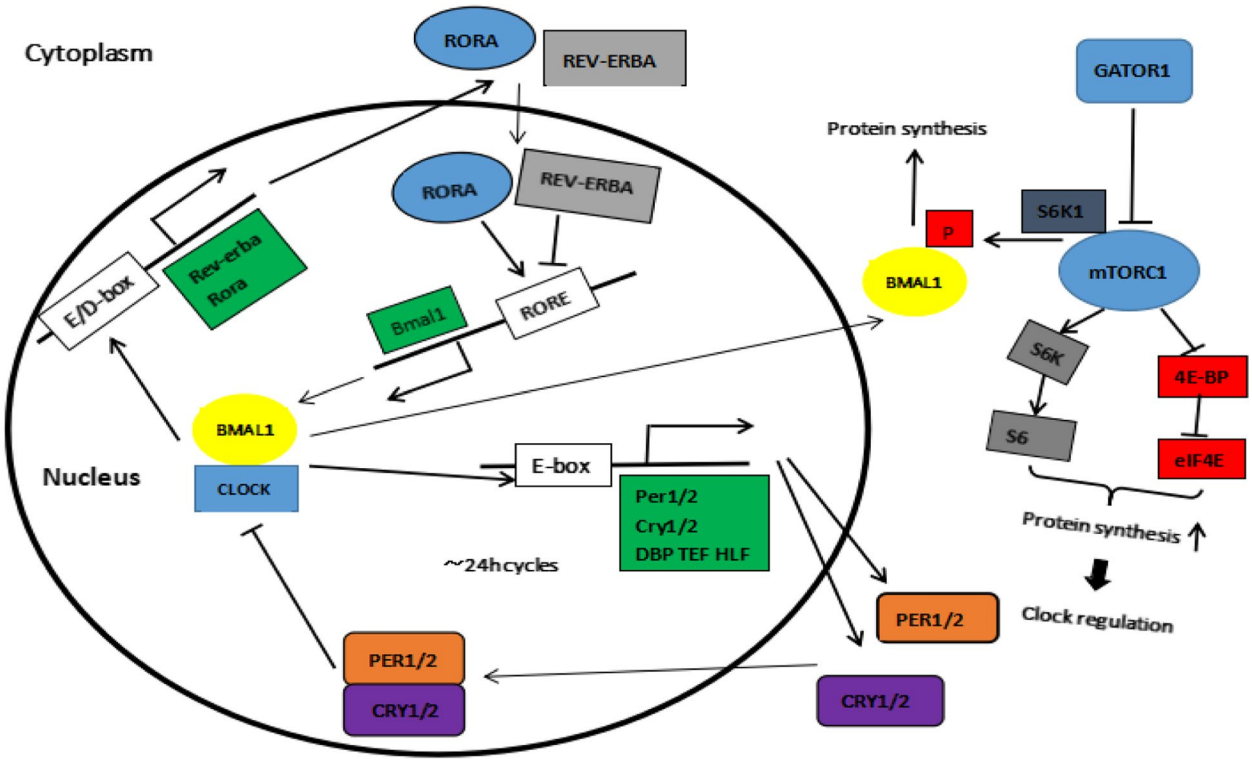

Fig. 1 A general overview ofmolecular mechanisms. There are two vital genes for the generation of thecircadian clock in the SCN cells, Clock gene and Bmal1 gene. The protein products of thesegenes form a heterodimeric CLOCK/BMAL1 complex in the cytoplasm. The CLOCK/BMAL1 complex translocates to the nucleuswhere it binds to specific E-box motifs and then drives the transcription of target genesincluding *Cry1-2, Per1-3*, and other downstream genes (PAR bZIPtranscription factor genes *TEF, DBP, HLE*). The mRNAs of Pers and Crys are transcribed and thentranslated into PERs and CRYs in the cytoplasm. The increased PERs and CRYs dimerize and translocate into the nucleus where they reduce the transcriptional activityof the CLOCK/BMAL1 complex, resulting in restraint of their own transcription. Additional feedbackloops begin when the transcription of two retinoic acid-related organ receptor response elements REV-ERBA and RORA is activated by the CLOCK/BMAL1 complex. The protein products of REV-ERBA(repressor of Baml1 transcription) and RORA (activator of Baml1 transcription)enter the nucleus where they competitively bind to the promoter of *Baml1* geneto stimulate the expression of Baml1. The GATOR1 complex can suppress theactivity of the mTOR pathway. The S6K1 kinase of the mTOR pathway can activate Baml1 *via* phosphorylationto regulate the function of BMAL1 and control circadian protein synthesis.mTORC1 regulates the phosphorylation-dependent S6K and eukaryotic translation initiationfactor 4E-BPs. The activated S6K stimulates S6 phosphorylation while 4E-BP1 phosphorylation causes its dissociation from eIF4E, which increasesprotein synthesis and then leads to a rapid clock system regulation. Clock =circadian locomotor output cycles, Bmal1= brain and muscle ARNT-like 1, Cry =Cryptochrome, Per1 = Period, TEF = translation elongation factor, DBP = D-box bindingprotein, RORA = RAR-related orphan receptor α, REV-ERBA = reverseerythroblastosis virus α, mTOR = mammalian target of rapamycin, GATOR1 = GAPactivity toward Rags 1, S6K1 = ribosomal S6 protein kinase 1, 4E-BP = 4E-binding protein, eIF4E = eukaryotic translation initiationfactor 4e

[79]. Therefore, the disrupted oscillatory expression of clock genes is associated with altered CR in epilepsy [83].

In addition, second feedback loops are also involved in the regulation of CR. The transcription of two retinoic acid-related organ receptor response elements including reverse erythroblastosis virus α (REV-ERBA) and ROR-related orphan receptor α (RORA) is activated by the CLOCK/BMAL1 complex, and the REV-ERBA and RORA proteins enter the nucleus where they competitively bind to the rev response element, the promoter of Baml1 gene, to modulate the expression of Baml1 [87]. Therefore, REV-ERBA (repressor of Baml1 transcription) and RORA (activator of Baml1 transcription) are connected with negative and positive circadian oscillation of Baml1 expression, respectively. Other auxiliary loops are also mediated by the REVA-ERB/RORA-mediated transcription of E4 promoter-binding protein 4 (E4bp4) gene and the CLOCK/BMAL1-mediated transcription of the Dbp gene. Their protein products (DBP and E4BP4) dimerize and bind to the D-box elements on the promoters of Rev-erbs/Rors, serving as an additional layer of regulation [90] (Fig. 1). A study investigating the expression of RORA in epileptic rats induced by pilocarpine showed that the RORA expression was declined in the

hippocampus at both acute and chronic phases [91], indicating that the RORA expression may contribute to the epileptogenic process possibly through its regulation of CR [92].

Under CR control, the mammalian target of rapamycin (mTOR) signaling pathway is a critical system that modulates cell functions (lipid and protein synthesis, proliferation and growth of cells) [93]. The GAP activity toward Rags 1 (GATOR1) complex can suppress the activity of the mTOR pathway. The ribosomal S6 protein kinase 1 in the mTOR pathway can phosphorylate thereby activating BMAL1 and control the synthesis of circadian proteins [94]. Moreover, mTORC1 regulates the phosphorylation of S6K and the eukaryotic translation initiation factor 4E-binding proteins (4E-BPs). The activated S6K stimulates S6 phosphorylation while 4E-BP1 phosphorylation causes its dissociation from eIF4E (eukaryotic translation initiation factor 4e), which increases the CAP-dependent translation and then leads to a rapid clock system regulation [95] (Fig. 1). Thus, the mTOR signaling pathway is involved in the modulation of functions of central and peripheral clock (amplitude and period) and the abnormal mTOR signaling may disturb the CLOCK/BMAL1 complex and its downstream products, resulting in epileptogenesis [14, 96]. Mutation of the GATOR1 complex and activation of the mTOR signaling pathway may both underlie the focal epilepsy [97, 98]. In addition, mTOR signaling inhibitors such as rapamycin and everolimus can reduce seizures in patients with tuberous sclerosis epilepsy [99, 100], which further support the role of the mTOR pathway in the epileptic seizures. Cdc42 that encodes cell division cycle 42 (GTP-binding protein) is associated with the mTOR protein [101]. It has been shown that Cdc42 influences the seizure threshold through the mTOR signaling pathway, which acts as a downstream target of Cdc42 [102]. Considering all these findings, the clock-related genes may contribute to structural epilepsy mediated by the mTORopathies, which may shed light into therapeutic approaches for epileptic patients, especially for structural epilepsy.

Circadian hormone pattern and epilepsy

After receiving direct environmental signal (light) from the retinal photoreceptor via the retinohypothalamic tract (or via the geniculohypothalamic indirectly), SCN transmits the signal to the pineal gland, which then secretes melatonin in a circadian pattern. The release of melatonin is at a high level during the dark period (peak at 2:00 am) and at a low level during the light period [103]. Melatonin can also act as an internal nighttime signal for the circadian system as the length of night is positively correlated with the duration of melatonin secretion [104]. Melatonin can modulate CR through activating the melatonin receptors (MT1 and MT2) in the central biological clock. Thus, melatonin can feed back into a central oscillator to affect rhythms in a SCN-dependent manner while its secretion is also modulated by the SCN clock. Disrupted circadian fluctuation of corticosterone levels has been displayed in mice with MT1 receptor knockout [105].

Notably, melatonin has a variable but prominent action on epilepsy. In patients with intractable epilepsy, the level of baseline melatonin is low during the interictal period while a high level of salivary melatonin would occur during the postictal period [106]. Furthermore, melatonin receptor whose expression depends on light and melatonin which regulates the circadian rhythms, has demonstrated an obvious change of secretion amplitude in epileptic rats with a decrease at zeitgeber time (ZT) point 0 for MT1 receptor and an increase at ZT18 for MT2 receptor, which may compensate for the severe epileptic condition [106]. Interestingly, pinealectomy significantly increases the seizure activity and facilitates epileptogenesis in a penicillin-induced model [107]. In addition, exogenous melatonin has been shown to exert beneficial effects against seizure in numerous experimental and clinical studies [108, 109]. However, the anticonvulsion effect of melatonin remains controversial. Melatonin exerts a proconvulsive effect at high doses while possessing an anticonvulsion action at lower doses [110]. This dose-dependent switch of effect may be because that melatonin at low doses can increase cortical and hypothalamic GABA levels, while high doses of melatonin reduce the GABA level in these regions [111]. This result also indicates a possible time-dependent response of melatonin. Interestingly, it has been found that melatonin has diurnal variation of susceptibility to the pentylenetetrazole-induced seizures accompanied by the lowest kindling threshold at night [112]. Agomelatine and ramelteon, novel analogues of melatonin, possess anticonvulsant effects in many experimental epilepsy models [113, 114]. However, on the other hand, agomelatine is ineffective in preventing epileptogenesis in a kainate acid-induced epilepsy model although it can suppress inflammatory factors and has neuroprotective effects against neuronal loss and gliosis [115]. Thus, although melatonin and its analogues show a potential anticonvulsion property, extensive research is still needed to clarify their effects in patients with epilepsy.

SCN also has a rhythm of cortisol secretion mediated by the hypothalamic-pituitary-adrenal (HPA) axis in a circadian pattern. The cortisol pulses reach a peak in the morning, and then gradually decline during the day, reaching a low trough at the end of active periods [116]. HPA dysfunction and rapid changes in cortisol level are involved in signal transduction and epileptiform seizure

of circadian rhythm [117]. In addition, it has been found that the levels of ACTH and cortisol are lower in the CSF of infants with infantile spasms than in normal infants [118]. ACTH and corticosterone have been considered as the first-line drugs to treat infantile spasm while traditional ASMs have difficulty to control seizures in patients with infantile spasm [119]. This cortisol concentration has an important role in the homeostasis of neuronal excitability and inhibition. With the gradual reduction of ACTH and cortisol after sleep, cerebral cortex inhibition is gradually diminished, which increases the probability of seizure occurrence in epileptic patients [120]. The levels of ACTH and cortisol are lowered in chronic epilepsy, increasing the secretion of corticotropin- releasing hormone (CRH) as an enhanced negative feedback. It is worth noting that CRH, an excitatory neuropeptide, can reduce the seizure threshold, resulting in seizure occurrences [121]. Furthermore, cortisol can improve the GABA level to reduce the neuron excitation through inhibiting GABA uptake by synapses and promoting the rapid synthesis of GABA [122]. In future studies, application of exogenous cortisol or measurement of endogenous cortisol levels can help further reveal the effects of circadian cortisol variability on seizure activities, using high temporal-resolution EEG recording.

Seizure prediction

The use of advanced techniques could advance the understanding of the relationship between epileptic activities and circadian rhythm, facilitating accurate seizure prediction. With accurate seizure prediction, seizure risk can be reduced and drug-related side effects attenuated by applying ASMs at differential dosing times. Moreover, patients and caregivers can also take some measures to avoid specific situation where seizures tend to occur at a certain time, if mathematical predictability algorithms are available. Thus, mathematical predictability models should be developed to predict the circadian fluctuation of seizure susceptibility based on age, sleep-wake pattern, rest-activity state, hormones, and seizure type. A previous study showed that combination of the temporal distribution of seizures with chronic intracranial EEG signals improved the seizure forecasting by algorithms [123]. In addition, the accuracy of seizure-forecasting algorithms will be enhanced by addition of multidien IED rhythms because the seizure occurrence also displays a multidien rhythm [42]. Nevertheless, it is difficult to generally apply this invasive device in the epileptic population; this prediction is feasible only when the benefits of detecting seizures outweigh the risk of neurosurgery for implantation of the intracranial device. Furthermore, the negative and positive predictive values of the forecasting algorithms are still not fully suitable for clinically meaningful prediction. Thus, further studies are needed to investigate the novel non-invasive and accurate devices (such as the wearable detection device); meanwhile, the factors that could affect seizure activities such as age, seizure type, and seizure origin zone should be considered. The rapid growth of clinical databases, and the integration of learning algorithms into wearable detection devices may help develop closed-loop systems and improve seizure- prediction models [124, 125].

Chronotherapy

Epileptic chronotherapy, which is a treatment strategy of drug administration at times of higher seizure susceptibility, can enhance the efficacy and reduce the side-effect of ASM. Apart from optimizing the administration timing of ASMs according to the circadian rhythms, the pharmacokinetic characteristics should also be taken into account, including the absorption, metabolism, distribution and elimination of the drugs [14]. This chronotherapy has been applied in several chronic diseases with a circadian pattern, including epilepsy [126]. One study investigated whether clobazam treatment tailored to the timing of seizures could improve seizure control in 27 epileptic patients. In this study, higher-evening differential dose of clobazam achieved better seizure control in patients with predominantly nighttime and early-morning seizures, possibly because the differential dosing provided higher overall treatment doses at times of greatest seizure occurrence without increased side-effects at other times [127]. Another study found that a chronotherapeutic dosing schedule of carbamazepine and phenytoin involving administration of most or all daily doses of ASM at 8:00 p.m. can improve seizure control than standard treatment regimens [128]. In 17 patients with nocturnal or early-morning seizures, taking a higher ASM dose at bedtime than in the morning led to seizure freedom in 64.7% (11/17) of patients and 88.2% (15/17) experienced $\geq$50% reductions of seizures, along with only 11.8% of patients experiencing fatigue [129]. Just like the closed-loop diabetes pump treatment, closed-loop detection-treatment systems may be a better choice for patients with epilepsy, especially for refractory epilepsy. Development of portable devices can decrease EEG recordings and hospital appointment, allowing for rapid detection of seizures and immediate treatment of patients. For generalized tonic-clonic seizures, some algorithms have proven useful in clinical practice [130]. However, a large-scale clinical trial of closed-loop chronotherapy has not been successfully conducted. Further studies are still needed to investigate the value of closed-loop chronotherapy in clinical practice.

Resetting the disturbed circadian rhythms may improve seizure control as the potential mechanism

underlying the circadian pattern of seizure occurrence is associated with dysregulation of clock genes. Melatonin and its analogues display a potential anticonvulsion property, probably due to their capacity to synchronize the disrupted circadian rhythms. However, there are inconsistent reports on the effect of melatonin on seizure control across different studies, even in systematic reviews. Light, as a crucial environmental cue, can reset the endogenous rhythms possibly because it can synchronize the clock system, even after a quick exposure [131]. In a randomized control trial, the light therapy significantly reduced symptoms of depression and anxiety in focal epileptic patients [132]. Another double-blinded randomized trial reported that the bright light exposure significantly reduced the seizure frequency in patients with drug-intractable epilepsy, but also induced seizures in patients with extra-TLE [133]. Clinical data on light therapy are still limited, which reinforces the necessity for further clinical studies to evaluate the specific effects of light therapy in epilepsy management. Ketogenic diet (KD), a high fat and low carbohydrate diet, also shows anticonvulsant and antiepileptogenic effects for intractable epilepsy [134]. In Kcna1-knockout mice that experience seizures with impaired circadian behavior, KD reduces the seizure frequency and restores the disturbed diurnal rhythmicity, which may be because that the diet, similar to light cue, can gradually reset the phase of rhythmic gene expression [135]. Moreover, KD exerts the anticonvulsant or antiepileptogenic effect possibly via inhibition of the mTOR pathway [136]. When circadian clock systems that regulate essential cellular and physiological processes are disturbed, the risk of epileptogenesis and seizure frequency would rise. Developing a 'clock drug' targeting the altered clock components or clock-associated cellular pathways is a novel therapeutic strategy for clock-related diseases. Fortunately, several small molecules have been identified as clock modulators that regulate the circadian pattern and the physiological outputs in disease models [137], which may be used as novel therapeutic agents or coadjuvant agents for epileptic patients in the future.

Limitation and direction

Despite great research progress on the relationship between circadian rhythm and epilepsy in animal models, there are also limitations that hinder translation into clinical practice. It is difficult to verify that the seizure occurrence is influenced by the circadian rhythm, sleep-wakefulness state, or light-dark cycles in humans, because it is challenging to apply specific protocols such as consistent light-dark cycles or consistent routine protocols in epileptic patients. Many confounding factors (e.g., ASM treatment, psychiatric comorbidities, and genetic variations) may also limit the observational results in clinical studies. Although the chronotherapy has been applied in a few animal models and in epileptic patients, the individual nature of epilepsy may affect the popularity of chronotherapy. Given the inter-individual variability of seizure occurrence, a large-scale patient-based tracking of seizure cluster would be advantageous in integrating the individual seizure patterns into accurate closed-loop systems. Despite the emerging evidence at the cellular and molecular levels, our knowledge regarding the relationship between epilepsy and circadian rhythm from the microcosmic perspective is far from enough, limited mainly at the brain network level. Thus, further large-scale studies are needed to assist prediction and treatment of circadian seizure activities and address these restrictions.

Conclusions

With the application of long-term video EEG and implantation of closed-loop neurostimulator system, our knowledge on the interaction between circadian rhythms and epilepsy has been greatly enhanced. It has been found that sleep-wake patterns, circadian timing systems and multidien rhythms have an essential role in seizure activities and IEDs. For instance, seizures and IEDs occur preferentially at the sleep state especially in the NREM stage, and sleep deprivation after the morning also increases the seizure risk. In addition, epilepsy type, seizure type and seizure onset zone significantly affected the rhythm of seizure occurrences, which should be considered into the seizure forecasting algorithms for accurate prediction. Apart from the effect of sleep on the occurrence of seizures of common epilepsy types, several specific epilepsy syndromes have a close correlation with the sleep-wakefulness patterns such as JME, BECTs, ADNFLE, LKS, BECOP, and ESES. Sleep influences the epilepsy rhythm and epilepsy in turn alters the sleep rhythm via the pathway of epilepsy *pe se*, seizures activity, comorbid sleep disorders and the effect of ASMs. Clock-related genes accompanied by two feedback loops of regulation play an important role in cortical excitability and seizure occurrence, which may be involved in the mTORopathies. These are considered as a useful model for advancing understanding of how the clock genes affect seizure occurrence and inspiring epileptic gene therapies in the future. SCN forms a rhythm of secretion of melatonin and cortisol under the circadian pattern, which then form a feedback as a central oscillator to affect rhythms, exerting variable but prominent actions on epilepsy. A time-dependent hormone therapy may be a potential option for epileptic patients, although their anticonvulsive action remains still controversial. Deeper understanding of the relationship between epileptic activities and circadian rhythm may facilitate accurate seizure prediction.

Integration of prediction algorithms into closed-loop detection-treatment systems with non-invasive devices may be a better choice for individualized intervention. Furthermore, optional timing and dosing of ASMs, and resynchronization of disturbed CR (by hormone therapy, light exposure, KD, or novel small molecules) would be beneficial therapeutic strategies for epileptic patients in the future.

Abbreviations

Ach: Acetylcholine; ACTH: Adrenocorticotropic hormone; ADNFLE: Autosomal dominant nocturnal frontal lobe epilepsy; ASMs: Antiseizure medications; BECOP: Benign epilepsy of childhood with occipital paroxysms; BECT: Benign epilepsy with centrotemporal spike; Bmal1: Brain and muscle ARNT-like 1; CR: Circadian rhythm; CRH: Corticotropin releasing hormone; Cry: Cryptochrome; DBP: D-box binding protein; EEG: electroencephalograph; ESES: Electrical status epileptitus during slow wave sleep; FLS: Frontal lobe seizures; GATOR1: GAP activity toward Rags 1; HPA: Hypothalamic pituitary adrenal; IED: Interictal epileptiform discharge; JME: Myoclonic epilepsy; KD: Ketogenic diet; LKS: Landau-Kleffner syndrome; mTOR: Mammalian target of rapamycin; nAChR: Neuronal acetylcholine receptor; NREM: Non-rapid eye movement; REV-ERBA: Reverse erythroblastosis virus α; RNT: Reticular nucleus of the thalamus; RORA: RAR-related orphan receptor α; SCN: Suprachiasmatic nuclei; SWD: Spike-wave discharge; TEF: Translation elongation factor; TLS: Temporal lobe seizures; 4E-BP: 4E-binding protein.

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Competing interests

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