



Chronobiology of limbic seizures: Potential mechanisms and prospects of chronotherapy for mesial temporal lobe epilepsy

Daniel Leite Góes Gitai^{a,b}, Tiago Gomes de Andrade^c, Ygor Daniel Ramos dos Santos^b, Sahithi Attaluri^a, Ashok K. Shetty^{a,d,*}

^a Institute for Regenerative Medicine, Department of Molecular and Cellular Medicine, Texas A&M University, College Station, Texas, USA

^b Institute of Biological Sciences and Health, Federal University of Alagoas, Maceio, Alagoas, Brazil

^c Faculty of Medicine, Federal University of Alagoas, Maceio, Alagoas, Brazil

^d Research Service, Olin E. Teague Veterans' Medical Center, Central Texas Veterans Health Care System, Temple, Texas, USA

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ABSTRACT

Mesial Temporal Lobe Epilepsy (mTLE) characterized by progressive development of complex partial seizures originating from the hippocampus is the most prevalent and refractory type of epilepsy. One of the remarkable features of mTLE is the rhythmic pattern of occurrence of spontaneous seizures, implying a dependence on the endogenous clock system for seizure threshold. Conversely, circadian rhythms are affected by epilepsy too. Comprehending how the circadian system and seizures interact with each other is essential for understanding the pathophysiology of epilepsy as well as for developing innovative therapies that are efficacious for better seizure control. In this review, we confer how the temporal dysregulation of the circadian clock in the hippocampus combined with multiple uncoupled oscillators could lead to periodic seizure occurrences and comorbidities. Unraveling these associations with additional research would help in developing chronotherapy for mTLE, based on the chronobiology of spontaneous seizures. Notably, differential dosing of antiepileptic drugs over the circadian period and/or strategies that resynchronize biological rhythms may substantially improve the management of seizures in mTLE patients.

1. Introduction

Circadian rhythms are central properties of living organisms tailored to anticipate and dynamically respond to a cyclical environment. Changes enacted by alternation between day and night on factors such as light, temperature, sleep, food and other periodic ecological elements instituted selective pressures to the evolving life to develop intrinsic biological rhythms. The enormity of these interfaces is apparent from the widespread presence of circadian rhythms in nature, from bacteria to complex organisms, and its impact on many biological processes (Bhadra et al., 2017). Notably, the discovery of the molecular mechanism of circadian rhythms in flies in the mid 80's won the Nobel

Prize in Physiology and Medicine (2017), showing how fast and substantially the role of circadian rhythms has been integrated to the management of human health.

Transcriptional-translational feedback loops (TTFL) modulated at different levels control the circadian clock in eukaryotes (Takahashi, 2017) (Fig. 1). Several components of the mammalian clock are highly conserved in flies. The core-clock transcription factors BMAL1 and CLOCK heterodimerize in the cytoplasm and form BMAL1:CLOCK complex, which translocates to the nucleus and instigates transcription of target genes by interacting with E-box promoters. The target genes comprise the core clock-controlled genes (CCGS), *Period* (*Per1*, *Per2*, *Per3*) and *Cryptochrome* (*Cry1*, *Cry2*). The protein products of PERs and

Abbreviations: AED, anti epileptic drug; BDNF, brain derived neurotrophic factor; CCGS, clock-controlled genes; CK1, casein kinase 1; CLOCK, circadian locomotor output cycles kaput; Cry, cryptochrome; GO, gene ontology; ipRGC, intrinsically photosensitive retinal ganglion cells; KD, ketogenic diet; MT, melatonin receptors; mTLE, mesial temporal lobe epilepsy; mTOR, mammalian/mechanistic target of rapamycin; NFIL3, nuclear factor, interleukin 3 regulated; NPAS2, neuronal PAS domain protein 2; Per, period; RHT, retinohypothalamic tract; RORs, retinoid-related orphan receptors; RRE, rev responsive element; SCF, skp1/cullin/F-box protein; SCN, suprachiasmatic nucleus; SLA, spontaneous locomotor activity; SRS, spontaneous recurrent seizures; TFs, transcription factors; TrkB, tropomyosin receptor kinase B; TTFL, transcriptional-translational feedback loops

* Corresponding author at: Institute for Regenerative Medicine, Texas A&M Health Science Center, College of Medicine, 1114 TAMU, 206 Olsen Boulevard, College Station, TX, 77843, USA.

E-mail address: shetty@medicine.tamhsc.edu (A.K. Shetty).

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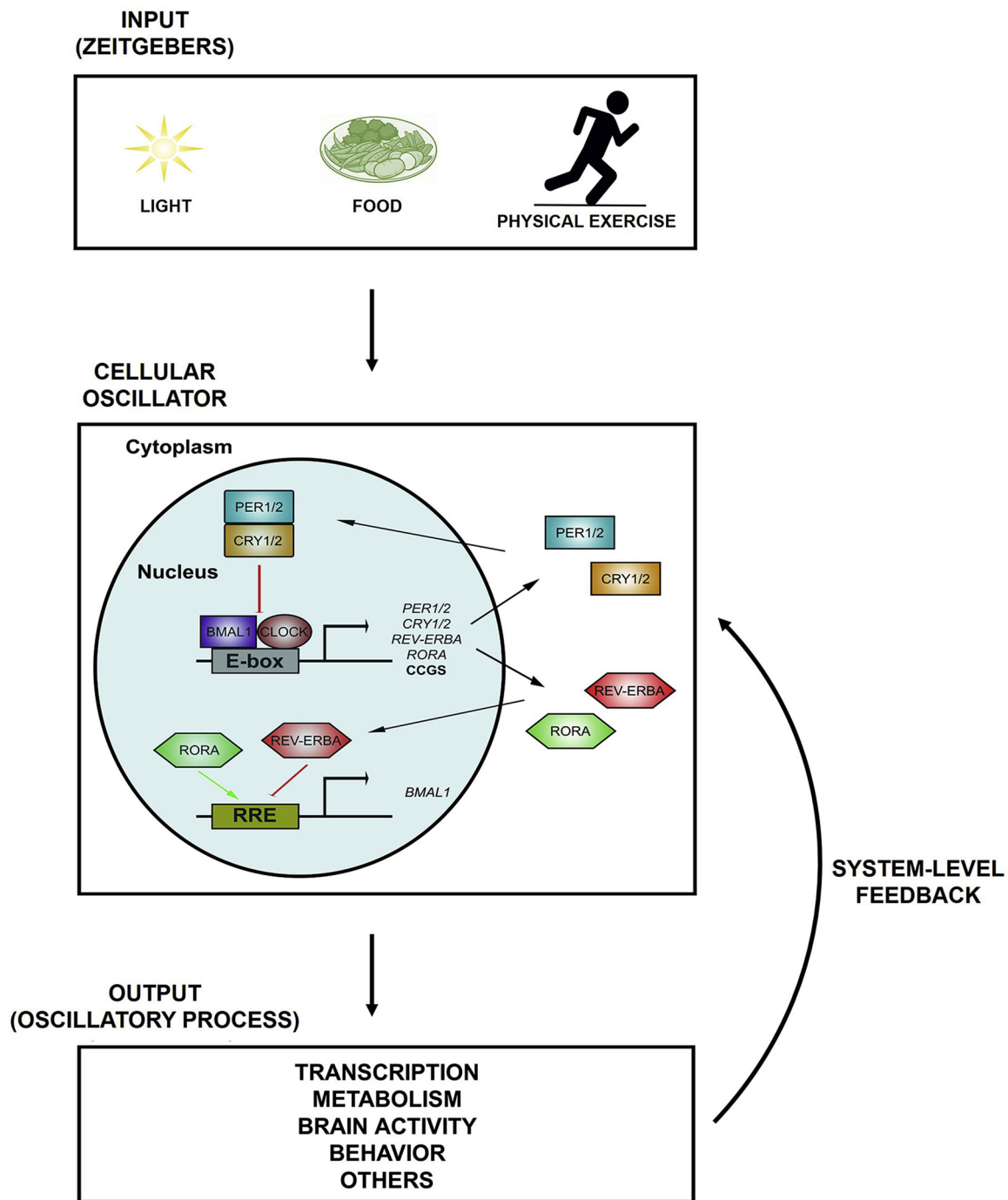


Fig. 1. A general overview of the molecular control of circadian rhythms. Synchronizing inputs such as light, food, and exercise modulate the endogenously generated circadian clock present in the central oscillator (SCN) or the peripheral oscillators throughout the body. The middle panel shows the cellular clock pathways. By interacting with E-box promoters, the BMAL1: CLOCK complex instigates transcription of target genes, period (PER1/2) and cryptochrome (CRY1/2), which leads to the formation of PER: CRY heterodimers in the cytoplasm. The activity of BMAL1: CLOCK complex is regulated through translocation of PER: CRY heterodimers into the nucleus. BMAL1: CLOCK heterodimers also activate the transcription of two retinoic acid-related orphan receptor response elements, RORA (activator of BMAL1 transcription) and REV-ERBA (repressor of BMAL1 transcription). Both RORA and REV-ERBA bind to rev responsive element (RRE) present in BMAL1 promoter to regulate the expression of BMAL1. The rhythmic outputs may also feedback to the cellular clock adding another level of temporal regulation in a multicellular system.

CRYs fluctuate across the 24-hour cycle by inhibiting their promoters operating in a complex negative feedback loop. Specifically, the PER:CRY heterodimers translocate into the nucleus and restrain their transcription by reducing the activity of the BMAL1-CLOCK complex. The accumulation of PER:CRY proteins is modulated through phosphorylation by Casein Kinase 1 (CK1) and degradation by Skp/Cullin/F-box (SCF) ubiquitin ligases. An added regulatory loop is produced when

BMAL1:CLOCK heterodimers activate the transcription of two retinoic acid-related orphan receptor response elements, RORA (activator of BMAL1 transcription) and REV-ERBA (repressor of BMAL1 transcription). Both RORA and REV-ERBA partake in binding to rev responsive element (RRE) present in BMAL1 promoter to regulate the expression of BMAL1. Thus, RORA and REV-ERBA are respectively involved in positive and negative regulation of the circadian oscillation of BMAL1.

Box 1

Key terms in Chronobiology.

Amplitude: The difference between the peak or trough and the mean value of a wave. It is a measure of how the variable intensity changes in the circadian time.

Central or master oscillator: In mammals, the hypothalamic suprachiasmatic nucleus (SCN), which receives photic inputs from the retinohypothalamic tract (RHT) and nonphotic cues from other afferent inputs, systemically orchestrates the multiple endogenous rhythms in the brain and other tissues to environmental signals, particularly the light (LeGates et al., 2014; Ramkisoensing and Meijer, 2015).

Chronobiotic: An agent capable of influencing parameters of biological rhythms (e.g., the phase setting) (Reinberg and Ashkenazi, 1993).

Chronotherapy: A treatment regimen developed based on the circadian rhythms of the patient. It can be related to chronopharmacology or other manipulations of the body's clock or external cues (*zeitgebers*).

Chronopharmacology: Pharmacotherapy adjusted according to the internal biological time to maximize treatment efficacy and minimize side effects.

Circadian rhythm: A rhythm of physiological, metabolic or behavioral oscillations occurring in ~24 h. Circadian rhythms persist in constant conditions.

Circadian Time (CT): CT is a quantification of time as defined by an organism's endogenous circadian clock, without reference to any environmental regulators or *zeitgebers*.

(Core) Clock genes: Clock genes are components of the circadian clock, which intricately interact with each other and generate oscillations of gene expression. The protein products of clock genes are essential components for the generation and regulation of circadian rhythms.

Clock-controlled genes (CCGS): CCGS are genes regulated by the core clock genes (Wright et al., 2009). Rhythmic translation and function of CCGS ultimately underlie daily oscillations at a cellular and organismal level.

Constant darkness: It is an experimental procedure employed to estimate the circadian period and phase-shifting agents under environmental conditions of continuous darkness exposure (Wright et al., 2009).

Coupling: Coupling is a process by which two or more oscillators interact in a stable phase relationship. Synchronization occurs through coupling mechanisms. In this sense, the SCN is composed of a network of coupled oscillators (Hafner et al., 2012). Uncoupling occurs when two or more oscillators drive out of this phase stability (e.g., peripheral oscillators uncoupled from the SCN).

D-box: D-box is a transcriptional regulatory element (TTATG[T/C]AA) that participates in circadian rhythm regulation (Kumaki et al., 2008). It is a DBP/E4BP4 binding element.

E-box: E-box is a transcriptional regulatory element (CACGTG) that participates in circadian rhythm regulation (Kumaki et al., 2008). It is a CLOCK/BMAL1-binding element.

Harmonic periods: These are period lengths harmonic with the circadian rhythms (e.g., 24 h, 12 h, 8 h). Harmonics are cycles that fit an exact number of times into a major cycle, such as the 24-hour cycle.

Internal temporal order: It is an order of maintenance of internal synchronization among the central and peripheral oscillators within an organism.

Misalignment: A state in which the individual's sleep/wake cycle is misaligned to the biological night, or there is a misalignment between central and peripheral rhythms (Roenneberg and Merrow, 2016).

Period: The period is an amount of time for a cycle to be completed, returning to the same phase. For example, the distance in time between two consecutive peaks (or troughs, etc.) of a wave.

Peripheral oscillators: Refer to the circadian oscillators located in cells, tissues or organs outside of the SCN.

Phase: The phase is an instantaneous state of oscillation within a period (reference point), generally the acrophase (peak of a rhythm).

Phase shift: The phase shift is a displacement of oscillation along the time axis. Can be a phase advance or a phase delay.

Resetting: Resetting is a phase shift in clock gene expression due to a synchronizing agent able to restart the cycle.

Shift work: Shift work is a schedule of work involving non-traditional working hours, usually during the evening and night ("Dictionary of Circadian Physiology," n.d.).

Spontaneous Locomotor Activity (SLA): SLA is a spontaneous motor behavior resulting from the integrated neural activity, controlled by the circadian rhythm and measured as a rest-activity pattern (Tilson and Mitchell, 1984). SLA is a behavioral marker for circadian rhythm alterations.

Synchronization: Synchronization is a state in which two or more oscillators assume the same frequency due to mutual or unilateral influences ("Glossary | Centre for Chronobiology," n.d.).

Ultradian rhythm: Ultradian rhythm is an oscillatory biological process with a periodicity of fewer than 24 h.

Zeitgebers: Zeitgebers are inputs to circadian clocks that alter the timing of rhythmic biological oscillations (Wright et al., 2009).

Zeitgeber Time (ZT): It is a quantification of time defined with reference to environmental regularities or *zeitgebers* (Wright et al., 2009).

Furthermore, the Nuclear Factor, Interleukin 3 Regulated (NFIL3) gene represses the CCG, D-box binding PAR bZIP transcription factor (DBP), to regulate the rhythmic transcription of D-box elements containing genes, RORA, and ERBA (McDaniel et al., 2011). The occupancy of promoter sites by transcription factors (TFs) and RNA polymerase present a circadian pattern, regulating the transcription globally (Koike et al., 2012). It is estimated that up to 50% of the genome is transcribed in a circadian manner in different tissues, with high specificity for each

tissue (Zhang et al., 2014). The other post-transcriptional/translational mechanisms also regulate circadian rhythms (Kojima and Green, 2015).

Circadian rhythms in mammals comprise a multi-oscillatory system, in which practically every single cell displays an autonomous genetically programmed rhythm, coordinated by a master oscillator, the hypothalamic suprachiasmatic nucleus (SCN) (Honma, 2018; Takahashi et al., 2008). The SCN receives photic inputs from the retinohypothalamic tract (RHT) and nonphotic cues from other afferent

inputs, to orchestrate the endogenous rhythms to environmental signals (LeGates et al., 2014) (Ramkisoensing and Meijer, 2015). Intrinsically photosensitive retinal ganglion cells (ipRGC) expressing melanopsin transduce light signals, independent of the canonical forming image pathways, to the SCN, inducing the expression of *Per1* and *Per2* genes (LeGates et al., 2014). This photic input resets the circadian molecular clock in the SCN with consequent coordination of several oscillators in the brain and other organs, synchronizing the internal body clocks to the environmental light. Misalignments of these external signals and the internal clock, as occurs in shift workers, or alterations in the clock genes have been correlated with disruptions in the circadian rhythms and many metabolic and neuropsychiatric disorders (Ramkisoensing and Meijer, 2015); (Smolensky et al., 2016).

The circadian activity of several brain regions has been described in humans and animal models (Frank et al., 2013; Li et al., 2013; Rath et al., 2014). In the hippocampus, the inherent circadian timekeeping capacity is fundamental for rhythmic fluctuation of hippocampus-dependent memory and learning (Snider et al., 2018) as well as its plasticity, including patterning, spine density, generation of new neurons (adult neurogenesis) and long-term potentiation (Chaudhury et al., 2005; Ikeno et al., 2013, 2014; O'Callaghan et al., 2012; Tamai et al., 2008). Therefore, structural and physiological alterations in the hippocampus in certain disorders may be linked to complex interactions with the circadian system.

Epilepsy, typified by spontaneous recurrent seizures (SRS), is one of the most common neurological disorders (Devinsky et al., 2018). Mesial temporal lobe epilepsy (mTLE), characterized by the progressive development of the complex partial seizures originating from the temporal lobe foci such as the hippocampus, is seen in ~30% of epilepsy patients (Fisher et al., 1998). Cognitive, memory and mood impairments are the behavioral comorbidities in mTLE, which are associated with multiple adverse changes and plasticity in the hippocampus. These include substantially diminished normal hippocampal neurogenesis, continued aberrant migration of newly born neurons into the dentate hilus, dispersion of dentate granule cells, considerable loss of GABAergic interneurons, aberrant mossy fiber sprouting, chronic neuroinflammation, gene expression reorganization (Shetty and Turner, 1999; Hattiangady et al., 2004; Shetty et al., 2005; Romcy-Pereira et al., 2008; Vannest et al., 2008; Kuruba et al., 2009; Waldau et al., 2010; Hattiangady and Shetty, 2010; Long et al., 2017; Shetty, 2014). The interaction between circadian rhythms and epileptic seizure occurs in a bi-directional manner as evidenced by the influence of environmental zeitgebers (food and light) on both onset and severity of seizures (Cho, 2012; Mirzoev et al., 2012; Roberts and Keith, 1994; Stewart et al., 2001; Weiss et al., 1993), and by the influence of seizures on temporal oscillation of body temperature (Quigg et al., 1999), locomotor activity (Stewart and Leung, 2003), sleep architecture (Kothare and Zarowski, 2011) and hormones (Molina-Carballo et al., 1994; van Campen et al., 2015; Yalín et al., 2006). A remarkable feature of this crosstalk is that the seizures, although unpredictable, present a rhythmic pattern of occurrence in mTLE and animal models of mTLE (Hofstra and de Weerd, 2009). Discerning how the time control system and seizures influence each other is of great interest for not only understanding the pathophysiology of epilepsy but also for developing new therapeutic strategies.

In this review, we focused on mTLE to provide an overview of the temporal remapping of the hippocampus as a potential contributor to the rhythmic pattern of limbic seizures. Moreover, we discuss several studies that investigated the effects of circadian rhythm disturbances on the epileptogenic process to bring insights regarding the role of the circadian system on limbic seizures and its implication for chronotherapy in epilepsy. The key terminologies and phrases used in this review are defined in Box 1.

2. Potential mechanisms for the temporal pattern of limbic seizures

Circadian regulatory system modulates the occurrence of partial complex seizures in certain types of epilepsy, which is evidenced from observations that seizures have a time-of-day preference, depending on its origin (Durazzo et al., 2008; Spencer et al., 2016). Patients afflicted with mTLE display a 24-hour non-uniform distribution of seizure occurrence with either a unimodal (afternoon) or bimodal (early morning and afternoon) time peak (Kalevayas et al., 2011; Karafin et al., 2010; Mirzoev et al., 2012; Nzwalo et al., 2016). Since sex and age modulate circadian rhythms in both humans and animal models (De Nobrega and Lyons, 2018; Bailey and Silver, 2014; Yan and Silver, 2016; Díaz-Morales and Parra-Robledo, 2018), it is essential to consider their potential interference in the temporal pattern of seizures. Age and sex discrepancies influence the highest occurrence of seizures in mesial temporal sclerosis (Passarelli and Castro, 2015). However, in a recent study using a large dataset of unspecified epilepsy, no significant differences in temporal patterns were seen between men and women for seizure cycles at different time scales (Karoly et al., 2018). Thus, additional studies are necessary to examine the effects of sex and age on circadian rhythms and temporal pattern of seizures.

Spontaneous seizures in kainic acid and pilocarpine models of mTLE have been found to occur in a daily pattern with a peak incidence befalling between 2–4 PM in multiple studies (Arida et al., 1999; Bertram and Cornett, 1994; Cavaleiro et al., 1991; Matzen et al., 2012; Tchekalarova et al., 2010, 2011; Van Nieuwenhuyse et al., 2015). Although the comparison across species is complicated because of nocturnal habits of rodents, it is remarkable that most time peaks in both humans and animal models occur in the daytime period. Unraveling the components involved in ictogenic mechanisms related to circadian rhythmicity across species would likely suggest new strategies for epilepsy management. On the other hand, it is important to note that the investigations for detecting the seizure periodicity in humans were performed by using a population-based approach, reflecting the overlapping seizure peaks across heterogeneous populations. When transferred to the individual level, the comparison between time peaks from humans and experimental models is not straightforward. Indeed, the endogenous and environmental factors composing mTLE pathophysiology give rise to individual variability, ultimately leading to patient-specific seizure cycle patterns that deviate from the mean in some cases (Karoly et al., 2018). Studies using long-term 24/7 video-EEG combined with algorithms for periodicity analysis will allow a better characterization of biological rhythms of spontaneous seizures. A study in an experimental model demonstrated that the circadian periodicity of seizures persists in a constant darkness condition (Quigg et al., 2000), suggesting a dependence of the endogenous clock system for epilepsy threshold. As the temporal pattern of seizures progresses uniquely depending on the localization of epileptogenic focus, determining the temporal pattern of seizures in different conditions has considerable significance. In mTLE, it is likely that increased electrical activity in the hippocampus modifies the oscillation pattern of clock genes and uncouples central and peripheral oscillators (Fig. 2).

2.1. Dysregulation of clock genes and clock-controlled genes in the hippocampus

A recent study has shown that the circadian expression of the core clock genes *Bmal1*, *Cry1*, and *Cry2* persist in the hippocampus of epileptic animals (Matos et al., 2018), although with phase and amplitude changes. The dysregulation of core clock genes can affect the 24 h availability of molecules that play roles directly or indirectly in the electrical activity of the hippocampus with consequences on the occurrence, frequency, and duration of seizures. A higher and lower circadian amplitude of excitatory and inhibitory CCGs can cause rhythmic fluctuations in the inhibitory/excitatory balance (Matzen et al., 2012;

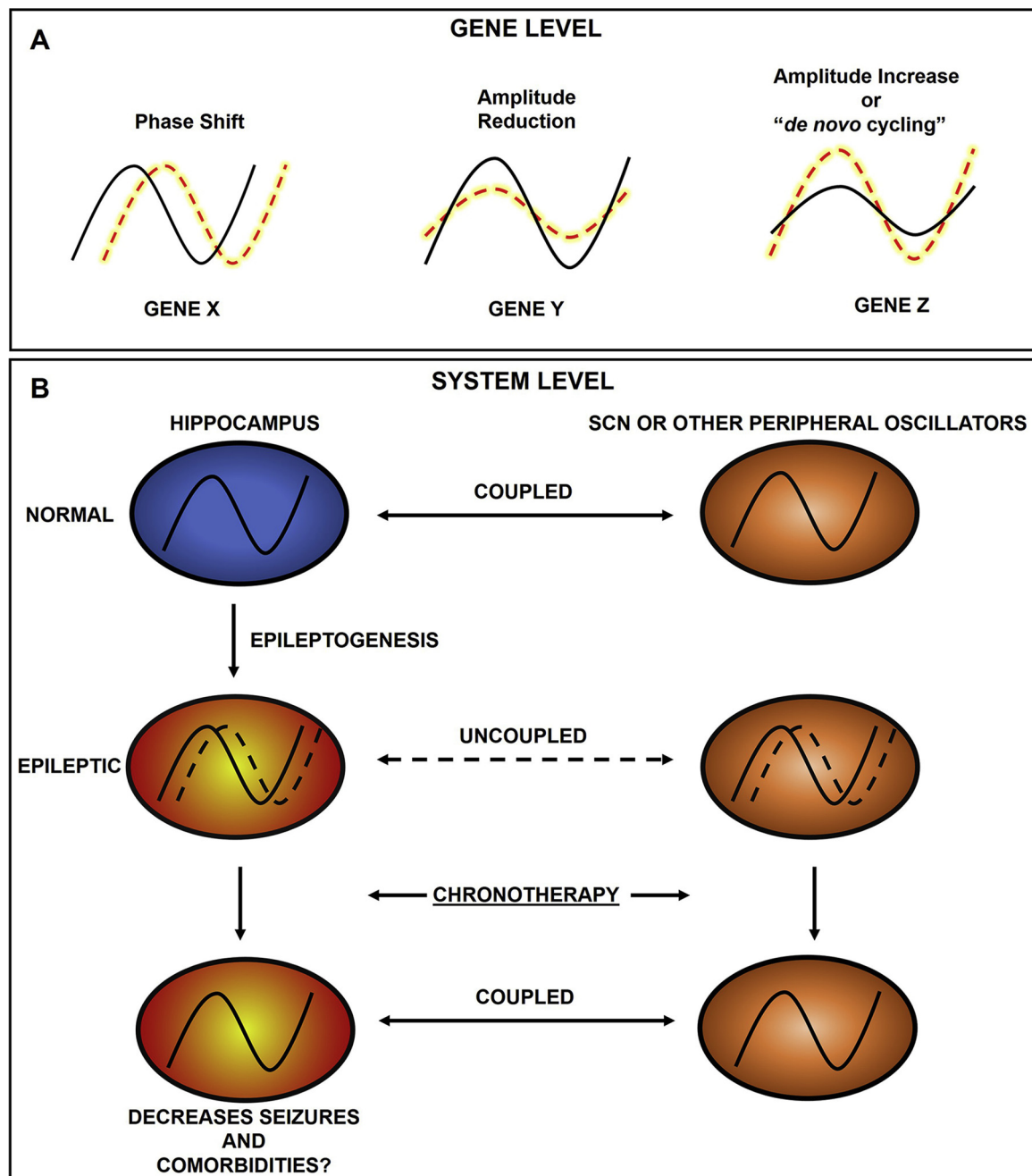


Fig. 2. Potential effects of epileptogenesis and chronotherapy on circadian rhythm parameters. At level of genes (A), distinct genes could be affected in phase and amplitude, changing the temporal transcriptome profile. At the system level (B), different oscillators may lose the stability in phase relationship due to changes in the temporal outputs from the hippocampus, uncoupling functional interconnected structures. A possible contribution of chronotherapy relies on resetting mechanisms that could restore the synchrony between the central (SCN) and peripheral oscillators.

Talathi et al., 2009). Accordingly, several studies have pointed out that seizure threshold and severity (Golombek et al., 1992; Roberts and Keith, 1994; Stewart et al., 2001; Weiss et al., 1993), as well as the anticonvulsant efficacy of antiepileptic drugs (Khedhaier et al., 2017), depends on the daytime or dark/light conditions. Essential regulatory systems involved in the modulation of seizure thresholds present circadian activity in the hippocampus including the melatoninergic (Musshoff et al., 2002) and the mammalian/mechanistic target of rapamycin (mTOR) pathways (Saraf et al., 2014).

Melatonin levels present higher amplitude in patients with epilepsy (Molina-Carballo et al., 1994) and the limbic seizures occur most frequently 6 h before the melatonin onset (Hofstra et al., 2011). Patients with intractable epilepsy have low baseline interictal melatonin levels

that increase dramatically following seizures (Bazil et al., 2000). Melatonin receptors (MT1 and MT2), which have an inhibitory effect on CNS, show a significant amplitude change (decrease at ZT0 for MT1 and increase at ZT18 for MT2) in the hippocampus of epileptic rats (Rocha et al., 2017). Both melatonin and agomelatine (an agonist of MT1 and MT2 receptors) have been reported to have anticonvulsant actions in models of acute and chronic seizures (Aguar et al., 2012; Dastgheib and Moezi, 2014). Also, RORA, a binding site of melatonin, has 24-h expression pattern in the hippocampus of control and epileptic rats (Rocha et al., 2016). Both mRNA and protein expression for RORA showed a decline in the acute and latent phases in the pilocarpine model. This pattern of expression may be involved in the epileptogenic processes. The ROR mRNA was also reduced in the chronic phase of

epilepsy (Rocha et al., 2016). It is highly likely that RORA contributes to the temporal pattern of limbic seizures as RORA is an essential component in the regulation of circadian rhythms (Solt and Burris, 2012) and has anti-inflammatory (Delerive et al., 2001) and antioxidant activities (Boukhoutche et al., 2006).

The mTOR signaling, engaged on a broader reorganization of gene expression (Laplanche and Sabatini, 2012; Solt and Burris, 2012), is overactivated in the hippocampus of both mTLE patients and animal models of mTLE (Tallos et al., 2018; Zeng et al., 2009). The inhibition of mTOR by Rapamycin results in both antiepileptic and antiepileptogenic effect in the mTLE model (Broekaart et al., 2017; Citraro et al., 2016; Huang et al., 2012). As the mTOR activity and its key products display circadian fluctuation in several tissues, with a higher peak during the day (Cao et al., 2010; Cao and Obrietan, 2010), the overstimulation caused by epilepsy could change the circadian oscillation of some downstream genes that act in excitatory/inhibitory balance. Investigating the temporal expression of these molecules in epilepsy models should bring valuable insights (Cho, 2012). Furthermore, a series of recent publications have shown that mTOR, which is regulated by the circadian clock (Hughes et al., 2009; Zhang et al., 2014), plays a significant role in regulating central and peripheral clock function including period and amplitude (Liu et al., 2018; Ramanathan et al., 2018). Interestingly, at night, when the limbic seizures are less frequent, there are high levels of melatonin and low activity of mTOR, suggesting that these systems may contribute to the temporal occurrence of seizures.

Chiang and colleagues conducted a quantitative proteome analysis of the normal hippocampus throughout a 24 h cycle from C57BL6/J male mice maintained in continuous darkness regimen (Chiang et al., 2017). They used JTK_CYCLE, an algorithm that identifies and characterizes cycling variables in large data sets (Hughes et al., 2010), to identify significant patterns of rhythmic expression at six time-points. The authors reported that 51 proteins out of 3052 displayed circadian rhythmicity. An individual functional annotation with QuickGO (Binns et al., 2009) revealed that Gene Ontology (GO) terms corresponded to central pathways in epileptogenesis, including *action potential* (GO:0001508), *positive regulation of neuron apoptotic process* (GO:0043525), *positive regulation of synapse structural plasticity* (GO:0051835), *positive regulation of cytosolic calcium ion concentration* (GO:0007204) and *neuron fate determination* (GO:0048664). Verification of these proteins against two epilepsy genetic databases (CarpeDB and epiGAD) and Pubmed (using the search terms “epilepsy OR seizure”) showed that 5 of them (*Cdc42*, *Chga*, *Gng3*, *Scarb2*, and *Sptan1*) have links to epileptogenic processes.

Remarkably, both *Cdc42* and *Gng3* have been shown to affect the seizure threshold. *Cdc42* encodes for cell division cycle 42 GTP-binding protein, which is involved in the regulation of neuronal structure (Bustelo et al., 2007; Govek et al., 2011). Moreover, *cdc42* protein is overexpressed in the hippocampus of mTLE patients (Xiao et al., 2007) and *cdc42* inhibition reduces seizure severity in the lithium/pilocarpine rat model of epilepsy (Zhang et al., 2015). The *cdc42* shows a lower expression peak at CT18 in the hippocampus, the time window displaying the lowest seizure frequency (early night) within 24 h. Furthermore, analysis with STRING database version 10.5, a repository that gathers information about physical and functional (indirect) protein-protein interactions (Szklarczyk et al., 2017), showed that *cdc42* protein has a functional interaction with mTOR protein (Combined score: 0.974). Indeed, mTOR is a downstream signaling target of *cdc42* (Chou and Blenis, 1996; Fang et al., 2003) and *cdc42* depletion inhibits mTOR activation (Endo et al., 2009). The anticonvulsant effect from both *cdc42* and mTOR inhibition (Citraro et al., 2016; Zhang et al., 2015) indicate a functional link between these proteins in the seizure threshold. *Gng3* encodes for G-protein gamma 3 subunit, which contributes to the specificity of receptor signaling pathways associated with a G-protein function (Schwindinger et al., 2004). Furthermore, *Gng3* knockout mice (*Gng3*^{-/-}) displays increased susceptibility to

seizures (Schwindinger et al., 2004), due to defective GABA_B receptor signaling (Schwindinger et al., 2011). The *Gng3* temporal expression profile reaches a peak at CT22, which are inserted in time window with the lowest seizure frequency (at night) within 24 h, implying the anticonvulsant activity of the *Gng3* protein in the hippocampus. Thus, changes in the expression of core clock genes in the hippocampus would result in modifications of the oscillatory expression patterns of CCGS acting on inhibitory or excitatory pathways, leading to a reduced threshold for seizure occurrence at precise times. The identification of harmonics of gene transcription in the brain (Hughes et al., 2009, 2012) may help in elucidating the mechanism behind the bimodal pattern of seizures in some TLE patients, with a reported ultradian seizure periodicity at 6–8 AM and 3–5 PM (Karafin et al., 2010). A recent study, using NeuroPace, Inc. RNS® System to monitor human interictal epileptiform discharges and seizures at protracted timescales, further demonstrated that all subjects exhibited a 12-h harmonic of the circadian rhythm and a multitude of other rhythms (Baud et al., 2018).

In mice maintained in continuous darkness regimen, 22 proteins were found with ultradian oscillation in the normal hippocampus (Chiang et al., 2017). Four of them (*Ncdn*, *Ptpnz1*, *Stx1b*, and *Calb1*) had been associated with epileptogenic processes in the hippocampus following status epilepticus. Nonetheless, analyzing the epileptic hippocampus with a higher temporal resolution is essential to confirm the ultradian pattern in gene expression. Evaluation of the temporal distribution of SRS through continuous video-EEG recordings in epileptic animals with knocked down of specific genes of interest would be ideal. Such analysis and in-depth characterization of the temporal expression of CCGS in an epileptic hippocampus would directly examine the potential time-dependent functional roles of genes in the generation/maintenance of SRS.

2.2. Uncoupled oscillators

The normal functioning of a multi-oscillatory system relies on the synchronization of the central and peripheral oscillators. Disruptions in this internal temporal order have been linked to multiple diseases (Smolensky et al., 2016). Hippocampus has intense connections with other brain structures, including direct neural pathways to SCN and other peripheral oscillators. As the clock gene *Per1* is responsive to electrical activity (Eun et al., 2011), the hyperactivity coming from the hippocampus could affect several circadian outputs leading to changes in amplitude or phase shifts. The clinical consequences of altered *Per1* expression (and other clock genes) in epileptic individuals are enormous as this could lead to extensive metabolism alterations and comorbidities linked with mTLE. Indeed, patients with epilepsy do demonstrate a wide variety of macrostructural sleep abnormalities (Derry and Duncan, 2013; Walker and Eriksson, 2011), such as sleep fragmentation and reduced sleep efficiency. Moreover, several functions controlled by the circadian clock are altered in epileptic individuals, including the hippocampus-dependent learning and memory.

The onset of spontaneous locomotor activity (SLA) has been shown to be unaltered in the mTLE model under light-dark conditions, suggesting that the SCN is appropriately responding to the light input (Matos et al., 2018; Stewart and Leung, 2003). However, the changes observed for some core clock genes in the hippocampus along with fragmented SLA (Matos et al., 2018) and body temperature (Quigg et al., 1999) rhythms may indicate a decoupling mechanism, in which the hippocampus and other oscillators are in different phase relationships compared to the healthy brain. The alterations in the hippocampus to SLA is likely linked to the activation of hippocampal-accumbens pathway after PILO-SE induction as demonstrated previously (Stewart and Leung, 2003). Alternatively, the seizures could modulate SCN-related functions, affecting SLA downstream (Quigg, 2000). If interacting oscillators are uncoupled, the input signals can reach their targets out of phase, modifying the structure in many ways. Inhibitory molecules may not have their receptors expressed at the right

time, or excitatory signals can reach the hippocampus in a low threshold condition (Fig. 2). Another possibility is a *de novo* circadian output effect, in which new genes could be rhythmically expressed due to the temporal changes in signal pathways. That is, the temporal inputs from other oscillators would not be in synchrony with the hippocampal timekeeping causing dysfunction in transcription of immediate early genes with a gain of oscillation for some targets (Fig. 2). A recent study using large-scale approaches provided an inventory of 1650 transcripts and 237 proteins undergoing diurnal expression in the hippocampus of a mouse model of mTLE (Debski et al., 2017). Notably, the authors observed that ~30% of the transcripts gain circadian fluctuation only when the brain becomes epileptic, which can contribute to *de novo* features of the limbic seizure rhythmicity.

A scenario combining multiple uncoupled oscillators superimposed in different phases may also lead to the arousal of harmonics in circadian seizure occurrence. Nevertheless, the potential contribution of circadian uncoupling to epilepsy still need to be addressed in future studies. In particular, assessment of circadian outputs in the hippocampus as well as in other brain oscillators would bring insights on the role of seizures as a disrupting cue for desynchrony with clinical consequences. Indeed, recent advances in techniques would likely help in the quantification of the oscillatory output *in vivo* and to determine a phase shift, amplitude of variation and periodicity over days. Such measurements have immense value to the epileptology field, especially for the implementation of chronotherapy in the future.

3. Chronotherapy for limbic seizures

Nearly 35% of mTLE patients acquire medically intractable epilepsy despite the availability of many medications over the last decade and adequate antiepileptic drug (AED) treatment (Kwan and Brodie, 2000). Furthermore, AED therapy is mostly focused on seizure reduction, which can lead to side effects even with a reduced frequency of seizures. Indeed, most mTLE patients display memory and mood impairments (Eddy et al., 2011; Schmitz, 2006). Only a minority of patients with intractable epilepsy qualify for surgical resection of the epileptic hippocampus, but this surgery is often associated with significant cognitive dysfunction (Helmstaedter et al., 2008). Hence, there is an urgent medical need for therapy that is efficient for both reducing the frequency of SRS and improving functions that are disrupted by seizures. Advanced knowledge on the involvement of the endogenous clock in the generation and sustenance of limbic seizures might shed light on the management of mTLE, a condition that has been recognized to be suitable for the application of chronotherapy. From these perspectives, it is plausible to implement an AED treatment regimen based on differential time dosing. Also, resetting the circadian rhythms in epileptic conditions may also be useful for reducing seizures.

3.1. Differential time dosing approach

By discerning the temporal pattern of seizure occurrence, one may design a drug administration regimen that would enable drug availability at times of higher seizure susceptibility, increased drug efficacy, and reduced toxicity. Such goals can be achieved by controlling both the time of drug administration and pharmacokinetic parameters under circadian control, including metabolism, excretion, absorption and distribution of the drug. By taking these variables into account, one may tailor drug schedules to improve their effectiveness by decreasing medication tolerance due to receptor holidays (Ramgopal et al., 2013). This kind of therapy is being investigated for several diseases with a periodic pattern of manifestation including some types of epilepsy (Manganaro et al., 2017; Tekade and Gattani, 2010). Overall, anti-epileptic chronotherapy with a differential dose of carbamazepine, phenytoin, clobazam has been shown to be more useful for seizure control without increasing adverse side effects, in comparison to conventional AED therapy (Amengual-Gual et al., 2018; Thome-Souza

et al., 2016; Yegnanarayan et al., 2006). While such studies have not been performed widely, they are nonetheless promising for suggesting guidelines that ensure the timing of drug activity during periods of maximal seizures. In this context, the development and the use of time-dependent drug delivery systems may gain priority for the pharmacotherapy of epilepsy (Singh et al., 2012). Moreover, studies on chronopharmacokinetic properties of AEDs in animal models of mTLE are critical for identifying optimal windows for dosing appropriate concentration of AEDs (Khedhaier et al., 2017). For example, it has been shown that carbamazepine level doubled around noon in rodents (Ramgopal et al., 2013). Furthermore, the identification of molecular rhythms in the mTLE model may provide new targets for AEDs (Debski et al., 2017).

3.2. Approaches for resetting the circadian rhythms

Since the potential mechanism for a periodic pattern of limbic seizures involves dysregulation of clock genes and uncoupling among the hippocampus and other oscillators, implementation of strategies that minimize harm from clock dysregulation/desynchronization could provide a new target in the management of epilepsy. In this context, application of external cues that reset endogenous rhythms may help in controlling the seizures and adverse effects. At the molecular level, this approach would induce changes in the amplitude or phase of core clock genes or their specific targets. Pharmacotherapy as a resetting approach has been applied in the circadian field to treat jet-lag, shift-workers and other sleep problems (Cuesta et al., 2015; Emens and Eastman, 2017; Lockley et al., 2015). The capability of this therapy to modulate phase, amplitude or period has the potential to be used in different conditions such as hypertension, immune disorders, mood dysfunction and aging (Chen et al., 2018; Portaluppi and Smolensky, 2010).

Melatonin is an endogenous chronobiotic molecule able to adjust altered circadian oscillation in several conditions perhaps due to its capacity to align the phase among peripheral and central oscillators (Sánchez-Barceló et al., 2011; Tchekalarova et al., 2015). Indeed, exogenous melatonin has been shown to have dose-dependent anticonvulsant actions and neuroprotective effects in several mTLE models and human patients (Petkova et al., 2014; Tchekalarova et al., 2013). However, studies evaluating circadian phase effect of melatonin or its agonists are scarce. Costa-Lotufo et al. (2002) examined melatonin treatment at two-time points (8:30 h and 17:00 h) in female rats. The authors suggested that the anticonvulsant effect of melatonin seemed to be more intense at the light-dark transition, but the differences were not significant statistically. Moreover, a few studies have shown a dose-dependent pro-convulsant effect of melatonin (Banach et al., 2011). These conflicting results reinforce the necessity for chronopharmacological studies that consider phase differences in melatonin responses. The mechanism of melatonin effects on epilepsy is likely multifactorial because melatonin can exert antioxidant and GABA-potential effects, in addition to its ability to synchronize disrupted circadian rhythms (Gupta et al., 2004; Kabuto et al., 1998; Niles et al., 1987).

Rapamycin, an mTOR pathway inhibitor, can both reduce seizures and modulate resetting of circadian rhythms occurring in SCN and peripheral oscillators in rodents (Liu et al., 2018; Ostendorf and Wong, 2015; Ramanathan et al., 2018). Clinical trials and case studies revealed a reduction in seizures with the use of rapamycin and other mTOR inhibitors, such as everolimus, in patients with tuberous sclerosis complex-associated epilepsy (Curatolo, 2015; French et al., 2016). The pre-clinical findings indicate that seizure-suppressive effect of rapamycin is maintained in the TLE model as long as rapamycin blood levels are sufficiently high (Drion et al., 2016). High doses and long-term treatment are likely necessary to achieve substantial anticonvulsant activity in human mTLE. Such regimens may give rise to unwanted side effects, however (Drion et al., 2016; Sliwa et al., 2012; van Vliet et al., 2012). Further clinical trials will be necessary to define the efficacy and

safety profile of rapamycin and other mTOR inhibitors for treating mTLE.

It has been shown that diazepam and valproic acid, two of the most used AEDs, change the phase of the core clock genes by increasing or decreasing their expression (Griggs et al., 2018; Johansson et al., 2011; Oggier et al., 2010). Moreover, based on the analysis of pharmacotranscriptome data available in DrugBank database version 5.0.6 (Wishart et al., 2018), it appears that phenobarbital treatment results in increased expression of *Per2* and *Per3* mRNA (Lambert et al., 2009). Additionally, several molecules have been discovered in screening strategies as clock modulators and could be used in the near future as new “clock drugs,” with the co-adjutant potential of resetting oscillators in epileptic patients (Chen et al., 2018; Wallach and Kramer, 2015). Whether or to what extent the chronobiological effects of AEDs contribute to the amelioration of limbic seizure frequency and severity remains an interesting topic for future studies. Besides, it is interesting to note that several *zeitgebers* have been reported to have an anti-epileptogenic role, including diet, light and physical exercise.

3.2.1. Diet

In mammals, feeding is a relevant cue for peripheral clocks including those in liver, muscle, pancreas and brain regions outside the SCN, regardless of the central clock (Damiola et al., 2000; Stokkan et al., 2001). This function is related to the role of specific nutrients (such as high-fat and high salt diet) and food factors (e.g., resveratrol) in resetting the cellular circadian clocks (Oike, 2017). The ketogenic diet (KD), a high fat, adequate protein, and low-carbohydrate diet, advances the onset of behavioral rhythms and disrupts the circadian clock (Challet et al., 1998; Oishi et al., 2009). Inhibition of mTOR pathway is likely one the mechanisms by which KD mediates these effects (McDaniel et al., 2011), which also involves the activation of peroxisomal proliferator-activated receptor γ (PPAR γ) (Simeone et al., 2017). PPAR γ is also linked to the control of the circadian clock (Chen and Yang, 2014) and hence a target for epilepsy treatment (San et al., 2015). Indeed, KD has been used as an antiepileptic treatment for some patients with drug-resistant epilepsy, but the underlying mechanisms of the KD action are still largely unknown.

Resveratrol, a grape polyphenol, can delay the phase of the circadian clock in cultured fibroblasts (Oike, 2017). Resveratrol also displays anticonvulsant activity (Ethemoglu et al., 2017) and has shown efficacy for easing SE-induced epileptogenesis (Mishra et al., 2015; Castro et al., 2017). Nonetheless, additional studies are required to elucidate the extent to which nutritional signals can reset peripheral clocks related to the antiepileptic action. From this perspective, studies in mTLE models assessing the anticonvulsant effects of specific nutrients and food factors by using a time-restricted approach would be helpful.

3.2.2. Light

Light is one of the most important cues that synchronizes the endogenous rhythms with the cyclic environmental changes occurring within 24 h. This role is likely due to its capacity for resetting the clock system even by quick flash exposures (Kaladchibachi and Fernandez, 2018). For example, artificial light has been used as an approach to realign endogenous rhythms within a therapeutic perspective, especially in sleep (van Maanen et al., 2016) and mood disorders (Geoffroy et al., 2018; Kaladchibachi and Fernandez, 2018; San et al., 2015). The mTLE could be a good candidate for testing this kind of therapy (Baxendale, 2011) since it has been shown that in individuals with this condition the biological rhythms are altered probably due to dysregulation of the clock system. Based on a double-blinded randomized control trial (Baxendale et al., 2012), it was observed that a periodic bright light exposure over 12 weeks reduced the seizure frequency during the treatment in patients with intractable epilepsy and the response was more effective in patients with hippocampal sclerosis. In another controlled trial, the same group observed that the bright light resulted in a significant reduction in symptoms of anxiety and

depression in patients with medically intractable epilepsy (Baxendale et al., 2013). Further clinical and preclinical studies are however required to evaluate the realignment of brain rhythms by the light as a therapeutic possibility for mTLE.

3.2.3. Physical exercise

Studies in humans and animal models have shown that physical exercise affects the SCN's firing rate and synchronizes circadian rhythms, acting as a non-photic cue (Mistlberger and Skene, 2005; Ramkisoensing and Meijer, 2015). Furthermore, several other studies have demonstrated that epileptic rats under different physical exercise regimen present a reduced number of seizures (Arida et al., 2004, 2007; de Almeida et al., 2017; Peixinho-Pena et al., 2012). Recently, it was shown that the antiepileptic effect mediated by physical exercise is related to elevated BDNF and decreased TrkB levels (de Almeida et al., 2018) in the hippocampus. Interestingly, the BDNF-TrkB has a vital role in the synchronization of endogenous rhythms to the 24-h light/dark by regulating the daily ultrastructural rearrangements of the neuronal-glia network in the master clock (Girardet et al., 2013) but not in the hippocampus (Ikeno et al., 2013).

4. Future directions

Collectively, the approaches mentioned above are supportive for investigating other ways of resetting the biological rhythms as a potential therapy for improving seizure control and ameliorating comorbidities observed in epilepsy patients. As mentioned above, many phase-resetting molecules have been uncovered by high-throughput screening *in vitro* (Hirota et al., 2008; Oike, 2017). Overall, they interact with clock proteins to alter period length or phase at the cellular level. Thus, the screening of these clock modulators as potential anti-epileptic agents can bring new perspectives for the treatment of mTLE. Alternatively, light, diet, exercise and other *zeitgebers* which potentially include cognitive plasticity (Gritton et al., 2012, 2013) could modulate the rhythms in the hippocampus and related structures with clinical benefits. Cognitive behavioral therapy has been applied for the treatment of epilepsy, with inconsistent results (Leeman-Markowski and Schachter, 2017; Tang et al., 2014). It would be interesting to investigate whether cognitive interventions at different phases could affect the rhythm in the hippocampus and modulate seizures more effectively.

Studies investigating the application of chronotherapy in mTLE or animal models of mTLE are still scarce to evaluate the suitability of time-specific therapeutic intervention regimens. However, this is not a straightforward approach, as the individual nature of epilepsy can influence its efficacy. From the perspective of inter-individual variability in seizure occurrence, a clinical protocol for chronotherapy must include a patient-based tracking of seizure clusters during the day. Such-tracking would help in incorporating the temporal patterns of seizures into individualized medication management.

Furthermore, transplantation of neural stem cells (NSCs) is being considered as a therapy for epilepsy and other conditions (Waldau et al., 2010; Shetty, 2011, 2014; Hattiangady and Shetty, 2012; Shetty and Hattiangady, 2016). Coupling of circadian rhythms to the cell cycle has been observed in NSCs, and clock genes have been shown to influence the proliferation and differentiation of NSCs (Malik et al., 2015; Akle et al., 2017; Draijer et al., 2018; Shimozaki, 2018). Therefore, the timing of NSC grafting or the use of synchronizers for aligning the clock system of grafted NSCs with the host NSCs in the neurogenic region may enhance the yield of graft-derived cells by stimulating the proliferation and differentiation of grafted NSCs. Indeed, a study demonstrated that melatonin-supported stem cell therapy is superior to the administration of stem cells alone (Lee et al., 2017). Regarding the application of NSCs for the treatment of epilepsy, grafting of the medial ganglionic eminence-derived NSCs into the hippocampus of rats exhibiting chronic TLE resulted in ~50% reductions in the frequency and

intensity of spontaneous seizures with no improvements in the memory function (Waldau et al., 2010). Analyses of grafts, however, revealed that the overall yield of graft-derived cells was ~28% of injected cells. From this perspective, grafting of NSCs into the chronically epileptic hippocampus along with circadian synchronizers, or phase-dependent grafting approach, may enhance graft cell survival and differentiation as well as host hippocampal neurogenesis, which may further diminish the frequency and intensity of spontaneous seizures, and alleviate memory and mood impairments seen in chronic TLE. Also, the use of circadian synchronizers in cell therapy may enhance the survival, differentiation and seizure-suppressing effects of other donor cell types considered for treating epilepsy. The cells include the GABA-ergic precursor cells from the embryonic brain, and GABA-ergic progenitors derived from the human embryonic stem cells and human induced pluripotent stem cells (Hattiangady et al., 2008; Hunt et al., 2013; Cunningham et al., 2014; Shetty and Upadhy, 2016; Upadhy et al., 2018).

5. Conclusions

Learning how the clock system modulates the seizure threshold is essential for comprehending the circadian occurrence of seizures and comorbidities as well as for developing innovative therapeutic approaches for mTLE. The temporal dysregulation of core clock genes in the epileptic hippocampus could affect the phase and amplitude of different genes that play roles in the electrical activity of neurons with consequences on the rhythmic fluctuation in the inhibitory/excitatory imbalance. As examples, the melatoninergic and the mTOR pathways are two essential regulatory systems in the modulation of seizure thresholds that present circadian activity in the hippocampus. Moreover, at the system level, the epileptic hippocampus could be uncoupled to other oscillators contributing in several ways to the occurrence of seizures as a de novo circadian output and to the extensive metabolic alterations linked with mTLE. From these perspectives, mTLE is a suitable condition for the application of chronotherapy for reducing seizures and comorbidities. Differential time dosing of AEDs and re-setting mechanisms by light, food, physical exercise or other approaches could be valuable strategies for the management of mTLE.

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