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Circadian rhythm in epilepsy: A brief note on clock gene expression

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ABSTRACT

Every cell in the human body is said to produce a cell specific rhythmicity, these rhythms are governed by the brains internal core clock. These rhythms are essential for maintaining day to day function of our body. These rhythms play a greater role in therapeutics as the drug perfusion in our body is time dependent. In neurology, a 24 hour rhythmic activity of epileptic seizure is a topic of greater interest. The rhythmic activity in epilepsy and seizure occurrence is related to the circadian variation in excitatory and inhibitory balance in neurons. There are two core circadian genes BMAL1 and CLOCK, that code for transcription factors, tend to influence the excitability and threshold of the seizure. Although there is uncertainties about the circadian rhythmicity that includes rhythm related factors such as time of the day seizure responses, frequency of occurrences of the seizures. In other cases the time of occurrences of the seizure is consequential to the severity of the seizures. However an improved seizure prediction can open new possibilities of research by understanding the efficacy of the treatment and the drugs used to control seizure. Better clarity on the severity and rhythmicity of the seizure can bring about newer and novel therapeutic options which can be beneficial in treatment of epilepsy. Lastly future studies in these area can clarify the seizure pathways involved in generating the rhythmic patterns in disease manifestation.

1. Introduction

The circadian rhythm is a part of internal 24-hour rhythm for nearly all the biological functions. The presence and effects of the circadian patterns in epilepsy has been recognised and studied for centuries. Many advances in technology such as long-term EEG recordings of brains neuronal activity, has greatly advanced our knowledge about role of circadian rhythmicity in epilepsy pathology.[1,2] Better understanding of the Circadian rhythm will lead ways in allowing more novel therapy and treatment process. Moreover, the advances in understanding of the circadian influences on neuronal excitatory and inhibitory mechanisms are easier by using EEG, these techniques can help to clarify the seizure generation and the inhibition of spread of seizure activity. This could also potentially lead to better treatment approaches, that included gene therapy and other opto-genetics tools for monitoring and controlling of the neuronal activity.[2] However with almost one third of the patients with epilepsy is being refractory to current treatment and drugs, there is a need for alternative treatment and approaches. The use of chrono-therapy, which is defined by therapies that are timed to by phases or time period of the circadian cycle can lead to better treatment plans and strategy for epileptic patients.[3] In this review can describe how circadian rhythms can affect the seizure activity in different lobes of the brains and seizures can control the sleep– wake states. These mechanisms are independent of the vigilance state of the seizures.[4] We can also understand and evaluate the efficacy of how the field of chrono-epileptology will contribute to diagnostic and novel management strategies, that could

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potentially transform our understanding of the patients with epilepsy.[5,6]

1.1. Sleep modulation and circadian rhythm

The modulation of EEG characteristics results in sleep –wake changes and cortical excitability during sleep.[7] The circadian system affects the brain function that are relevant to epilepsy in different ways possible ways: Firstly the system will contributes to the regulation of the timing of sleep and wakefulness along with its phases. Secondly it modulates the brain function during sleep and wakefulness during epilepsy episodes.[8,9] While we consider that these two different pathways can help with the interpretation of cortical excitability and temporal patterns in seizure activity.[10] Especially during sleep the synchronisation and desynchronisation with in the thalamocortical networks will takes place through a synchronous discharge at the regions of the thamalic nucles, this helps in generation on Non rapid eye movement NREM sleep oscillations and spike wake discharges and sleep spindle generation.[11] Cortical excitability is also modulated by the circadian phase, such that it results in more reduced in the evening hours than the day. The Diurnal changes in neuron behavioural performance is the result of slow regulation of cortical excitation and inhibition, which is depends on the circadian timing. The monitoring of neuronal activity for a longer periods of time (from months to years), thus sheds light on the relationship between interictal epileptiform discharges (IEDs), epilepsy, and circadian rhythms.[12–18] Specifically the IEDs peaked at sleeping hours independent of the location in the cortex. The seizures occurred with varied circadian patterns, seizure onset timing and zone.[19] Although IED activation is principally see during the sleep, the transition from the pre ictal to the interictal to the ictal state is modulated by circadian factors, with the effects seen related to the epilepsy type and severity of the epilepsy.[20]

2. Pathophysiology

The pathophysiology of epilepsy has a mainly contributes to the dysfunction of channel membrane excitability and excitatory and inhibitory imbalance of the neurotransmitter at the neuronal level.[9] In animal epilepsy models studies, the expression of many neurotransmitter receptors GABA and ion channels that are voltag–dependent channels are studied under the circadian regulation.[21] Many studies that use ligand-binding assay techniques have shown an increased circadian variability in the ion channels and neurotransmitter activities in the cortex and the hippocampus structures of the brain.[12,22–24] In conditional epileptic mouse models, deletion of the core CLOCK gene in the regions of excitatory neurons and not in the inhibitory neurons led to a lower seizure threshold and relatively better sleep characteristics and sleep quality.[25] The loss of the CLOCK gene in the mice models resulted in altered electro-physiological properties of the neuronal circuitry and reduction of the dendritic formation. This alteration leads to the depolarisation effect and shift of the paroxysmal events which can be considered the hallmark of epilepsy.[11] The CLOCK genes in the suprachiasmatic nucleus, is called the central circadian pacemaker. However it will remains preserved and there is normal regulation of sleep–wake in these mice.[15,24] In many cases the seizure excitability may be a direct effect of loss of the CLOCK function at the cortical neurons of the brain, than that which is mediated by suprachiasmatic nucleus activity due to a disease. The BMAL1 gene, are responsible for the binding partner of CLOCK gene to form the transcriptional CLOCK–BMAL1 complex, which is also directly involved in epilepsy.[12–17] The Deletion of BMAL1 in the cells can abolish the circadian variability of the induced generalised seizures in an animal model.[20] In addition, the absent of BMAL1 is known to reduces seizure levels in BMAL1 knock-out mice than that of the wild-type mice, many research suggest that the BMAL1 contributes to seizure excitability.[26] It is considered to focus more on the Treatments that target the interaction between circadian regulation and seizure pathways can be a promising options for patients with structural epilepsy and sleep-related seizures.[17]

3. Discussions

The Unpredictability of the seizure occurrence is often highlighted as one of the main reasons that affects quality of life in epileptic population.[27] In the recent past Chronotherapy, harnesses the knowledge of optimal medication, aiming to strike a balance between desired effect and side-effects in order to increase the efficacy of the treatment, has been applied in several therapeutic and treatment paradigms for recurrent or chronic health conditions.[17] The optimal timing and usage of dose in chronotherapy, usually requires a usage of a biomarker for feedback of the dose titration and response. This is proven to be very efficient in many chronic conditions.[28–35] A very obvious treatment strategy in epilepsy is monitor the greatest occurrence of seizures and treat the patient during higher seizure occurrences, which can be based on the retrospect increased epileptogenicity with respect to the time of wakefulness and sleep. In most cases the circadian, infradian, and ultradian or multidien rhythmicity is taken into consideration.[21] But understanding the seizure rhythmicity it becomes beneficial in predicting the patterns of seizures that occurs at a specific time, this can help in administering the peak doses of anti-epileptic drug during the peak occurrences.[12] Although there are many input loops are that is being evaluated, such as seizure detection using watches and wearable gadgets, maintaining a dairy and closed-loop clinical tracking of the patients in understanding the seizure rhythmicity.[36–40] The discovery

of Biomarkers in epilepsy involves the selection of EEG parameters which analysis the cortical excitability in the brain cells.[22] This is a brief recording done for a substantively amount of time to understand the excitability of the neurons and contribute greatly in assessment and diagnosis of epilepsy.[26,28,29] There are many treatment trials based on measurements of EEG abnormalities need to be performed; these trials would provide promising opportunities for diverse treatment application. They throw a better clarity on using of high doses of medication during higher seizure susceptibility, uses of effective combination drugs, uses of localised systemic medication pumps, receptor or circuitry modulation. These methods can be proven to be more effective in seizure control. In Several studies have considered the of uses of hormonal therapy including melatonin to improve sleep quality which can thereby control the seizure ; however, results from these studies are conflicting, and has not brought out a substantial evidences of seizure control using melatonin.[28]

4. Conclusions

In the review we have a series of studies that present an increasing rate of evidences that supports the underlying mechanism that sleep-wake related patterns and epileptic seizures occur in a 24 hr circadian rhythm. Studies have also shown the multidien rhythmicity of the seizures that corresponds to the 20-30 day seizure recurrent pattern in epilepsy.[10–20] In both the circadian system and homoeostatic Regulation of the sleep cycle, there is an alteration of sleep structure, cortical excitability, awakening time and period of wakefulness.[7] These factors might have a stronger role in epileptic seizure susceptibility. The increasing seizure occurrence in the morning, nocturnal seizure during sleep and sleep deprivation are more likely to be related to an increasing in cortical excitability and a circadian excitability in morning hours.[14] It is clearly understood that sleep, epilepsy and circadian rhythms are inter related.

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6. Conflict of Interest

The author declares that there is no conflict of interest.

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