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Review Article

Review on the mechanistic links between sleep characteristic changes and epileptogenesis

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ABSTRACT

Sleep and epilepsy are known to have a bidirectional interaction. Although sleep is differentiated into Rapid eye movement and Non Rapid eye movement sleep, Further gets classified into different stages based on the electroencephalogram EEG traces. Sleep is popularly studied using a Polysomnogram (PSG) which is the golden standard in measuring sleep metrics. In 1929 using an intervention with electroencephalography (EEG) made better contributions to objective investigations and clinical observations for unravelling further reasoning. Although there is an increasing evidences of sleep disturbance in most cases of epileptic syndromes the sleep interaction methods are very poorly reasoned out. Using invasive intracranial EEG the evidences obtained on cortical activities of the deep and superficial brain structures are given evidences on the interaction mechanisms of sleep and epilepsy. The sleep spindles are phasic events seen in non –rapid eye movement sleep in mammals. The sleep spindle is relevant in many aspects of brain activities such as sleep quality, memory consolidation, aging and mental health. In the last decade one of the most important understanding the interplay between how spike wake discharge is modulated by the slow sleep waves underlining the role of epileptic activity to sleep .These studies helped to demonstrate how different seizure types affected by sleep and how epileptogenic zone can be better identified for epilepsy surgery. This article will review the influence of sleep in epileptic brain and its significances using an EEG.

1. Introduction

Gibbses[1] in his atlas as described the relationship between sleep and epilepsy, mentioned the interictal epileptic discharge (IEDs) enhancement in NREM sleep .Many authors summarised the relationship between the spike wave discharge and seizures across various sleep stages in different epileptic syndrome.[1–5] Growing research and knowledge about sleep physiology in the recent past have interested many in understanding the roles of sleep in epilepsy. It found that NREM sleep helps in the synchronisation of several brain functions like memory consolidation, synaptic homeostasis, Vigilance regulation and also mental health rejuvenations process.[4–9] In the last 4 decades the view on epilepsy has changed in many aspects. Although having the term focal or generalized has become increasingly difficult, however there was no clear classification of the epilepsy forms. The newer concepts of systems epilepsy offer a broader frame for classification and taxonomy purposes. The increasing evidences support that epilepsies tend to transform functionalities of the brain.[10–15] Epilepsy is called an heterogeneous condition, as it has various triggers such as genetic abnormalities, brain lesions that cause a physio – patho mechanism which leads to various epileptic syndromes.[16–21] During the epilepsy developmental period,the epilepsy transformation

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typically causes dysfunction in brain structures that involved in sleep function such as fronto-thalamic and cortico-thamalic systems (The cortex and thalamus has an inter relation that links the transition point between a quiescent and abnormally epileptic state".[17,22] We shall try to trace epileptogenesis in four sleep-related major epilepsies, in order to explore the inter-relationship between epilepsy and NREM sleep.[21–25]

2. Sleep and Sleep-SpecificBrain Signalling

Sleep is considered a phenomenon that affects the functioning of the brain simultaneously and uniformly.[26–28] In the recent researchers it is said that sleep is locally modulated phenomenon and there is a number of cortical and thalamic synchrony involved in sleep in the brain.[28] One of the most convincing data evidences was obtained during a pre surgical epilepsy evaluation which used the local modulation of the central sleep control of human using an iEEG.[29–31] Recent research advances have shown evidences of certain brain regions exhibiting awake like activities even during the transition phase from wakefulness to sleep even during N3 sleep stages.[21,24–28] The important sleep-specific oscillations in the brain are sleep spindles. The sleep slow oscillations are <1 Hz and delta wave activity is between 1-3 Hz. Sleep spindles are distinctly present in the EEG events; they are the hallmark of Non Rapid Eye Movement NREM N2 sleep stage. They can be differentiated with frequency between 10 -15 Hz with duration between 0.5 – 2 s with a diphasic oscillations.[31–34] Sleep spindles are important attributes for sleep stability, cortical development and memory consolidation.[35,36] Sleep oscillations are rhythmic alternation that can be characterized by depolarization state and polarization state of the cortical neurons, the activation between the cortical neurons cause the slow oscillation in the sleep stages.[33] Similar to the sleep spindles, k complexes are found in N2 sleep stage of NREM. They play a functional role in information processing, sleep and arousal however there role on sleep stabilization is still unclear.[35,36]

3. Interictal Epileptic form Discharge in Sleep

In the early 60s Gibbs and Gibbs literatures suggests that focal interictal epilepsy biomarkers are strongly influenced by sleep .We shall understand how an IED is classified as a epilepsy EEG biomarker and High frequency oscillation >80 Hz (HFOs) is also included as a new bio marker for epileptogenic zones in focal epilepsy.[34] IEDs are characterised as brief epileptic events lasting <200ms mostly without clinical symptoms. In a meta-analysis includes a EEG studies which comprised a total of 1458 patients in comparison to REM sleep the focal IED was higher in wakefulness specially in N3 than N2 and N1 sleep stages, But present at all the three stages.[34–36] This data indicates the rates of discharge are higher in NREM sleep in N3 and comparable between wakefulness and REM sleep. Not only there is a rate of increase in IEDs but also wider cortical spreads during the NREM sleep.[33] This phenomenon can be explained well by increased EEG synchronization in slow wave oscillation in the brain during NREM sleep and increased De synchronization during REM sleep.[34] High frequency oscillations are considered to be promising new markers of the epileptogenic zone. HFOs is identified as isolated events with the least four Consecutive oscillations > 80 Hz. The frequencies are further distinguished as faster ripples >250 Hz and ripple between 80 - 250 Hz.[36] HFOs are considered non-pathologic, but tend to occur under physiological conditions and are reported depending on the localization.[36] In order to develop normalisation values of intracranial EEG activity, carefully selected iEEG channels that shows normal physiologic EEG activity i) exclusion of a significant slow wave during recording, ii) activity outside of lesion tissue as assessed with imaging and iii) absence of interictal activity in the recording period.[1,33] Physiologic ripples > 80 Hz were seen to be frequent in cortical areas, with higher rates in the occipital cortex, basal and medial temporal region, transverse temporal gyrus, pre- and postcentral gyri, planum temporal, and medial parietal lobe. In contrast, the physiologic fast ripples 250 Hz are inexistent, which makes it suitable for defining the epileptogenic zones Physiological HFOs attributed a role for sleep-dependent processing of cortical neuronal networks, task processing and memory consolidation. Similarly to the distribution of HFO and IEDs are highest during NREM sleep, and lowest during REM sleep and wakefulness.[36] The rate of HFOs differs independently of the sleep stage in the seizure-onset zone.

4. Sleep and the Epileptogenic Zone

The Knowledge in sleep electrophysiology is relevant for clinical neurophysiology. This is become important in the prolonged video-EEG monitoring, which is necessary for pre surgical epilepsy evaluation. There is a hypothesis that the epileptic activity in temporal lobe epilepsy is focally confined during REM sleep than compared to NREM sleep.[37] The IEDs present in REM sleep can be localizing, as they occur only in brain regions with higher incidence of epileptogenicity, In which inhibitory influences of de-synchronization of neurons are affected by the pathological malfunctioning. HFOs have become very important aspects in analysis of sleep. The Coupling effect of sleep-specific transients can further contribute to increase of HFOs in epileptogenic zone, as it might help to understand the patho-physiology.[38,39]

5. Sleep and Circadian Rhythm

The tendency of seizures that occur at specific periods of the day is known, but its contribution for sleep and wake cycle and circadian rhythm in general is quiet unclear. There are multiple studies in the recent past that has identified specific time points at which the seizure activity increase in both adults and children.[40–42] There are different epileptogenic regions may vary with respect to their ictal period, the data obtained for these studies are taken during epilepsy monitoring. There are many studies that show circadian peaking of seizures from different brain lobes,ie focal seizures the time varies throughout the 24 hr/ day.[43] While the circadian mechanism of each seizures varies with time, Frontal lobe seizures occur mostly in the mornings, occipital seizures peak in the early evening and very rarely occur during sleep and temporal lobe seizures have two diurnal peaks, morning and late afternoon (evaluated under a non-circadian environment).[8,12,23] In a study analysing a total of 1800 seizure types shows that the focal seizures occurred often in NREM sleep and lowest during REM sleep. On the contrary most of the studies consisted of nocturnal sleep recordings only, instead of seizure during wakefulness .This may have led to the underestimation of seizures occurring during wakefulness. However the nocturnal seizures are related to have more severe and longer hypoxemia effects, and more mostly followed by postictal EEG suppression, these factors are implicated in sudden unexpected death in epilepsy.[44] Epilepsy not only modulates the sleep wake rhythm, but also influences the circadian rhythm. There is a link between phase shifts in secretion of hormones such as melatonin in epilepsy. Also a decreased expression of core clock genes such as BMAL 1, Per, Clock that are involved in circadian rhythm regulation is dsyregulated during epilepsy.[40–43,45]

6. Discussion

In summary, we discuss the influence of sleep on epilepsy from a neurophysiology stand point. Although there is a substantial progress in the last few decades, many aspects needs to be further clarified and understood for better understanding of the patho-physiology. Currently the future research scopes the way to understanding the sleep of the patient before surgery for any epileptic disease.[18,23,34] Sleep recording can now be used to analysis and evaluate to be new biomarkers for epileptogenesis. The better understanding of REM sleep with less suppression of epileptic activity can also be further discussed.[27] Another interesting research area is to understand the different pathways by which seizures are linked to different phases of the circadian rhythm and sleep-wake cycle in epileptic syndromes . This can also inform of newer and novel treatment and therapy option, also promote chrono therapy for epilepsy treatment. Epileptic transformations can be considered as an innate distortion of critical brain functioning that can be associated with sleep plasticity. In epileptic population we can find effects on sleep with respect to changing epilepsies and its effects on the circadian rhythm. We can consider post injury seizures to be a better model to understand sleep effects and restoration of normal sleep patterns post-surgery. The understanding of sleep to arousal and shifting stages of sleep in the twin-systems is a peculiar factor. This can help in identifying the mechanism of those epilepsies, understanding the normal functioning without triggering a seizure response. Another interesting link between arousal parasomnias and nocturnal epilepsy is worth discussing. Most of the nocturnal epilepsies are frontal lobe epilepsies. However the first one is to understand a sleep disorder and the second is the epilepsy seizures, but they have similar seizure episodes and sleep-relatedness symptoms, and they are said to share a common genetic background. Both conditions these conditions present a microarousal-related sleep dissociation mechanism, with high rate of motor and autonomic arousals that co-occurs in the dorso frontal networks of the brain.

7. Conclusion

We know the role of NREM sleep in epilepsy from the aspects related to sleep-related homeostasis .The increased excitability may reach a paroxysmal (epileptic) level causing a seizure. However we are unclear whether the role of NREM sleep that is seen in epileptic syndrome can apply to epilepsy that originates during the adulthood. These models of changing epilepsies from childhood to adulthood can bring about dysfunction of various clock genes that are involved in circadian regulation of our body. This condition also paves ways for various models to understand the epileptogenesis in general.

8. Conflict of Interest

The researcher claims no conflict of interest.

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None.

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