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Review Article

Review on circadian rhythm the role of core clock gene expression during sleep in epileptic syndrome

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ABSTRACT

Circadian rhythm is a 24 hour or a day's rhythmic oscillations with physiological and behavioural changes that is internally governed by the brain. This activity is generally anticipated by the internal and external cues from the environment. In circadian rhythm of our body is regulated by a transcriptional –translational Auto-regulatory loop which leads to the molecular oscillations of our "core clock genes" at a specific cellular level. In the many mammalian and animal models, the master pacemaker is in the hypothalamus at the suprachiasmatic nucleus (SCN) that can regulate downstream oscillations in the peripheral tissues of the brain. The core clock genes are self- sustained and cell autonomous not only on the pace maker but also on the other dissociated cultured cells and peripheral tissues. Here we can review the general mechanisms involved in the clock genes that is responsible for the circadian rhythmicity in epileptic syndromes and these findings can elucidate the cell specific expression of the clock genes in different syndromes. In the recent past there has been considerable amount of progress in elucidating the molecular and cellular mechanisms that is involved in understand the core clock gene expression and the circadian rhythms effects on epileptic syndromes. However, there is very little understanding on how these two mechanisms interact to cause a core clock genes disruptions plays an important role. Recent studies in several animal models have shown the effects of time of the day on the neurophysiology and path-physiology in the epileptic syndrome. Together, these evidences from the past suggest that there can be a common mechanism underlying the circadian rhythmicity and epileptogenesis mechanism.

1. Introduction

The circadian rhythms are very basic phenomena that is seen very obviously in all living organisms. They are influenced by factors called zeitgebers,[1–5] they regulate various physiological process such as body temperature, cell cycle, feeding, metabolism and sleep –wake cycle and other cellular level activities. The very obvious relationship between circadian rhythm and epilepsy is far less understood.[6,7] The effects of the time-of-the-day effects and circadian rhythm disruptions on epileptogenesis has been learned for many decades, and there has always been a renewed level of interest in accounts of better understanding of the gene level, molecular level and structural level understanding of the complex interaction mechanism.[8,9] In many epileptic disorders the disruption of the circadian rhythms and interrupts the expression of core clock genes and cell specific signalling cascades that experiences the time-of-the-day cycle. Along with epileptic behaviour, these cell specific expression brings out environmental, behavioural, genetically and pharmacological resistances in many cases. The efficacies of Anti-epileptic drugs reduce due time-of-the day effect. Given the importance of the natural 24-hour light–dark cycle, an increased emphasis of the most common functional relationship between circadian

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rhythms and epilepsy has a broader implication in treatment and prognosis in epileptic population.[10] In many animal model studies we have first describe the time-of-the-day neuronal activity and molecular pathways that are governed by the central pacemaker.[11–13] Secondly, we present the work that shows the circadian dysfunction in brain cells that causes alteration of physiological processes that includes the synaptic plasticity (such as long-term potentiation) and on seizure propagation in nocturnal (at night) and diurnal (at day). The cyclic pattern of the molecular cascades are involved in seizure propagation, while the cyclic activation and reactivation of these molecular cascades are over the 24-hours, ideally 25 hours.[14,15] They are independent inputs of the core time-keeping cells that contribute to locomotors rhythm outputs.[16] This Review article will expand on previously understood concepts of circadian effects on behavioural and physiological level, by considering the recent data that show the involvement of circadian rhythm in sleep phenomenon of specific molecular pathways in epileptic syndromes.

2. Core Clock Gene Involvement in Circadian Rhythm

The circadian clock is responsible for the regulation of a wide variety of physiological and behavioural processes throughout an approximately 24 hour cycle.[17] While the circadian clock can have a number of hierarchies of oscillators. First is the suprachiasmatic nucleus (SCN) of the anterior hypothalamus in the brain. The SCN is responsible for the coordinating of all independent peripheral oscillation so there is a coherent rhythm.[18,19] The organization of the core clock mechanism in the SCN and the peripheral oscillators are said to be similar in function at the molecular level.[19] The SCN consists of a network of TTFL transcriptional– translational feedback loops that are known to drive rhythmic, 24-h expression of gene patterns of core clock components.[20] The Core clock components are defined by production proteins that are critical for the regulation, functioning and generation of the circadian rhythms within the every single cells of an organism.[18,19] The primary feedback loop, consists of two elements. In the positive elements there are the members of (bHLH) basic helix-loop-helix and PAS (Period-Arnt-Single-minded) transcription factor.[2–9] The CLOCK and BMAL1 genes are heterodimerize and they initiate the process of transcription of the target genes in containing the E-box cis-regulator and enhancer sequences, this includes the Period and the Cryptochrome (Per1/Per2/Per3/Cry1/Cry2) in the mice.[21–23] On the other hand the Negative feedback is achieved by the PER: CRY genes are heterodimers conjugation that is used in translocations in the nucleus to repressing the transcription by acting on the CLOCK: BMAL1 gene complex.[17,23] On the contrary, other regulatory loop are formed by CLOCK:BMAL1 heterodimers . They activate the transcription of the retinoic acid-related receptors.[23] These receptors subsequently end the process and the bind retinoic acid-associated receptor response elements that is present in Bmal1 gene promoter.[21]

The circadian rhythm oscillation of core clock gene Bmal1 in SCN of the brain is both positively and negatively regulated. This process is involved in the precision of the core clock genes, these affect the stability and nuclear translocation core clock proteins.[21] Casein kinase (CK11 and CK1d) places a critical factor in regulation of the core circadian protein accumulation.[17–23] In recent practices, an ubiquitin modifier protein is used in modification of BMAL1 in the post-translational regulation.[22] Casein kinase is said to have drastic effects on circadian periods of the post-translational functioning in the mechanisms of the circadian clock. Mutation of the Casein Kinase is said to have altered and caused alteration of circadian period in mammals. These mutations can also be seen in familial advanced sleep phase syndrome (FASPS) in human which results in altered sleep.[21]

3. Circadian Rhythms and Sleep in Epilepsy

Most of the data reviewed have a brief outline on the seizure occurring at different time period across the 24 hour circadian cycle.[24] Some of the seizure under studies (i). The temporal lobe seizures, the occurrence of seizures is syndrome specific, with different syndromes being more or less susceptible to the endogenous factors.[25] (ii). The Limbic seizures, is presented by mesial temporal lobe epilepsy and is seem in the animal models, occur mostly during the day and are slightly precipitated by sleep and other circadian cue or endogenous factors.[26] (iii) The frontal lobe seizures that are types of non-limbic and cortical focal seizure. The epileptiform discharges mainly occurs at the night and are more susceptible during the non-rapid eye movement sleep (NREM) sleep.[27] (iv)In the generalized epilepsy, such as juvenile myoclonic epilepsy, is predominantly occur in sleep–wake transitions phase, especially during the morning awakening.[28] In the recent studies one of the complexity is that the temporal seizure occurrences have made a summation of different rhythm influences in epileptic seizures The ultradian periods of recurrence or < 24 hours, infradian >24 hours, and circadian rhythms that accumulate to a polyrhythmic and complex pattern.[29]

4. Inter-ICTAL Discharges and Sleep

The effects of sleep characteristic changes in neurological conditions are known for long. Especially in epileptic syndromes, the interictal discharges alters the sleep characteristics and bring about a circadian rhythm dysfunction.[30–32] The common relationship between sleep and epilepsy are very closely studied in the last few decades, however it is still unclear how the seizures

bring out a time of the day peak during a 24 hour period. There are convincing evidence that recognizes sleep deprivation as a risk factor to seizures triggers. However Sleep deprivation is encouraged in some types of epilepsy for the diagnosis or pre-surgical assessments of epilepsy.[31] There are many epileptic syndromes that's has predominate EEG abnormalities which is seen only during sleep and its clearly evident that the sleep characteristics change due to the epileptic seizure .In Benign Childhood Epilepsy that presents Centrotemporal Spikes (BCECTS). It is the most common epileptic syndrome seen during infancy and it is considered to be a sleep-related epilepsy because of its 75% of all seizures occur only during NREM stages.[33–36] In many nocturnal seizures the generalization of seizures can be done. While the EEG is normal during the awake period and abundant spike or spike wave discharges is seen in NREM N1 and N2 sleep staging. In cases involving Benign Childhood Epilepsy that has Occipital Paroxysms. It is Childhood epilepsy with occipital paroxysms, which is blocked when the eye is open during wakefulness, is clearly considered another syndrome that causes sleep character changes.[36] During which there is an increase of paroxysms response. In Frontal lobe epilepsy usually presents seizures during sleep.[32–38] It is very important to make the correct diagnosis with certain parasomnias. The EEG findings are considered to be crucial evidences of seizures. The frontal epilepsy expresses a variety of clinical of clinical manifestations such as awakening, dystonia and complex motor behaviour. One of the most appreciated work on sleep and epilepsy is that when sleep facilitates the discharge in the prefrontal cortex, they are driven by the thalamocortical circuits that are sometimes associated with sleep spindle generation.

5. Conclusion

Since sleep typically occurs mostly during the "night". It is quite difficult to differentiate the effects of sleep and the epilepsy that causes disruptions in circadian cycle. Many experimental designs that potentially unlink the influential attributable to sleep–wake state transition to that of the biological clock Is studied in animal epileptic models.[39] While there is very few records of human model studied in order to know the circadian rhythm in epileptic populations. In general, during the NREM sleep there is the occurrence and spatial distribution of epileptiform discharges (IEDs); while in REM sleep tends to inhibits both.[38,40] Circadian Rhythm disruption from the molecular level tends to affect the sleep characteristics in syndromes

6. Conflict of Interest

The researcher claims no conflict of interest.

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References

1. Lowrey PL, Takahashi JS. Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annu Rev Genomics Hum Genet*. 2004;5:407–41. doi:10.1146/annurev.genom.5.061903.175925.
2. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002;418(6901):935–41. doi:10.1038/nature00965.
3. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. *Science*. 2000;288(5466):682–5. doi:10.1126/science.288.5466.682.
4. Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, et al. Period 2: Luciferase real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proc Natl Acad Sci USA*. 2004;101(15):5339–46. doi:10.1073/pnas.0308709101.
5. Folkard S, Wever RA, Wildgruber CM. Multioscillatory control of circadian rhythms in human performance. *Nature*. 1983;305(5931):223–6. doi:10.1038/305223a0.
6. Monk TH, Weitzman ED, Fookson JE, Moline ML, Kronauer RE, Gander PH, et al. Task variables determine which biological clock controls circadian rhythms in human performance. *Nature*. 1983;304(5926):543–5. doi:10.1038/304543a0.
7. Monk TH, Weitzman ED, Fookson JE, Moline ML. Circadian rhythms in human performance efficiency under free-running conditions. *Chronobiologia*. 1984;11(4):343–54.
8. Davies JA, Navaratnam V, Redfern PH. A 24-hour rhythm in passive-avoidance behaviour in rats. *Psychopharmacologia*. 1973;32:211–4. doi:10.1007/BF00428692.
9. Holloway FA, Wansley RA. Multiple retention deficits at periodic intervals after active and passive avoidance learning. *Behav Biol*. 1973;9(1):1–14. doi:10.1016/s0091-6773(73)80164-6.
10. Tapp WN, Holloway FA. Phase shifting circadian rhythms produces retrograde amnesia. *Science*. 1981;211(4486):1056–8. doi:10.1126/science.7193351.
11. Fekete M, Van Ree J, Niesink RJ, De Wied D. Disrupting circadian rhythms in rats induces retrograde amnesia. *Physiol Behav*. 1985;34(6):883–7. doi:10.1016/0031-9384(85)90008-3.
12. Gerstner JR, Lyons LC, Jr KW, Loh DH, Rawashdeh O, Eckel-Mahan KL, et al. Cycling behavior and memory formation. *J Neurosci*. 2009;29(41):12824–30. doi:10.1523/JNEUROSCI.3353-09.2009.
13. Takahashi JS, Hong HK, Ko CH, Mcdearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nature Rev Genet*. 2008;9(10):764–75. doi:10.1038/nrg2430.
14. Neurons and networks in daily rhythms. *Nature Rev Neurosci*. 2007;8(10):790–802. doi:10.1038/nrn2215.
15. Kandel ER. The biology of memory: a forty-year perspective. *J Neurosci*. 2009;29(41):12748–56. doi:10.1523/JNEUROSCI.3958-09.2009.
16. Silva AJ, Zhou Y, Rogerson T, Shobe J, Balaji J. Molecular and cellular approaches to memory allocation in neural circuits. *Science*. 2009;326(5951):391–5. doi:10.1126/science.1174519.
17. Balsalobre A, Marcacci L, Schibler U. Multiple signaling pathways elicit circadian gene expression in cultured Rat-1 fibroblasts. *Curr Biol*. 2000;10(20):1291–4. doi:10.1016/s0960-9822(00)00758-2.
18. Nagoshi E, Saini C, Bauer C, Laroche T, Naef F, Schibler U, et al. Circadian gene expression in individual fibroblasts: cell-autonomous and self-sustained oscillators pass time to daughter cells. *Cell*. 2004;119(5):693–705. doi:10.1016/j.cell.2004.11.015.
19. Welsh DK, Yoo SH, Liu AC, Takahashi JS, Kay SA. Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. *Curr Biol*. 2004;14(24):2289–95. doi:10.1016/j.cub.2004.11.057.
20. Brown SA, Fleury-Olela F, Nagoshi E, Hauser C, Juge C, Meier CA, et al. The period length of fibroblast circadian gene expression

varies widely among human individuals. *PLoS Biol*. 2005;3(10):e338. doi:10.1371/journal.pbio.0030338.
21. Takahashi JS, King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, et al. Positional cloning of the mouse circadian clock gene. *J Biol Rhythms*. 2004;19(5):339–47. doi:10.1177/0748730404269151.
22. Gekakis N, Staknis D, Nguyen HB, Davis FC, Wilsbacher LD, King DP, et al. Role of the CLOCK protein in the mammalian circadian mechanism. *Science*. 1998;280(5369):1564–9. doi:10.1126/science.280.5369.1564.
23. Kume K, Zylka MJ, Sriram S, Shearman LP, Weaver DR, Jin X. mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. *Cell*. 1999;98(2):193–205. doi:10.1016/s0092-8674(00)81014-4.
24. Gowers W. Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms and Treatment. William Wood; 1885. Wood's library of standard medical authors. New York: William Wood & Company; 1985. p. 157–64.
25. Quigg M. Circadian rhythms: interactions with seizures and epilepsy. *Epilepsy Res*. 2000;42(1):43–55. doi:10.1016/s0920-1211(00)00157-1.
26. Spencer DC, Sun FT, Brown SN. Circadian and ultradian patterns of epileptiform discharges differ by seizure-onset location during long-term ambulatory intracranial monitoring. *Epilepsia*. 2016;57(9):1495–502. doi:10.1111/epi.13455.
27. Baud MO, Kleen JK, Mirro EA. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun*. 2018;9(1):88. doi:10.1038/s41467-017-02577-y.
28. Quigg M, Straume M, Menaker M, Bertram EH. Temporal distribution of partial seizures: comparison of an animal model with human partial epilepsy. *Ann Neurology*. 1998;43(6):748–55.
29. Wallace E, Wright S, Schoenike B, Roopra A, Rho JM, Maganti RK, et al. Altered circadian rhythms and oscillation of clock genes and Sirtuin 1 in a model of sudden unexpected death in epilepsy. *Epilepsia*. 2018;59(8):1527–39.
30. Eriksson SH. Epilepsy and sleep. *Curr Opin Neurol*. 2011;24(2):171–6.
31. Lerman P. Benign partial epilepsy with centro-temporal spikes. In: Roger J, Dravet C, Bureau M, Dreifuss F, Wolf P, editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. London, UK: John Libbey; 1985. p. 150–8.
32. Beaumanoir A. Infantile epilepsy with occipital focus and good prognosis. *Eur Neurol*. 1983;22(1):43–52.
33. Pincherle A, Proserpio P, Didato G. Epilepsy and NREM-parasomnia: a complex and reciprocal relationship. *Sleep Med*. 2012;13(4):442–4.
34. Mayor L, Burneo J. Epilepsia y sueno. *Revista de Neuro-Psiquiatria*. 2002;65(2):142–54.
35. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, et al. Autosomal dominant nocturnal frontal lobe epilepsy: a distinctive clinical disorder. *Brain*. 1995;118(1):61–73. doi:10.1093/brain/118.1.61.
36. Zucconi M, Oldani A, Smirne S, Ferini-Strambi L. The macrostructure and microstructure of sleep in patients with autosomal dominant nocturnal frontal lobe epilepsy. *J Clin Neurophysiol*. 2000;17(1):77–86.
37. Guerrero GP. Epilepsia y sueno. *Acta Neurol Colomb*. 2008;24(1):21–4.
38. Beaumanoir A, Blume W. The Lennox-Gastaut syndrome. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari C, Wolff P, et al., editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. London, UK: John Libbey; 2005. p. 125–48.
39. Pavlova MK, Shea SA, Scheer FA, Bromfield EB. Is there a circadian variation of epileptiform abnormalities in idiopathic generalized epilepsy? *Epilepsy Behav*. 2009;16(3):461–7.
40. Tassinari CA, Rubboli G, Volpi L, Billard C, Bureau M. Electrical status epilepticus during slow sleep (ESES or CSWS) including adquired epileptic aphasia (Landau-Kleffner syndrome)," in Epileptic Syndromes in Infancy, Childhood and Adolescence. London, UK: John Libbey; 2005. p. 295–314.

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