Epilepsy Currents
2021, Vol. 21(2) 122-123

DOI: 10.1177/1535759721989672
journals.sagepub.com/home/epi
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Ticktock—What Is the Seizure Driving Clock?

The Circadian Dynamics of the Hippocampal Transcriptome and Proteome Is Altered in Experimental Temporal Lobe Epilepsy

Debski KJ, Ceglia N, Ghestem A, et al. *Sci Adv*. 2020;6(41):eaat5979. doi:10.1126/sciadv.aat5979

Gene and protein expressions display circadian oscillations, which can be disrupted in diseases in most body organs. Whether these oscillations occur in the healthy hippocampus and whether they are altered in epilepsy are not known. We identified more than 1200 daily oscillating transcripts in the hippocampus of control mice and 1600 in experimental epilepsy, with only one-fourth oscillating in both conditions. Comparison of gene oscillations in control and epilepsy predicted time-dependent alterations in energy metabolism, which were verified experimentally. Although aerobic glycolysis remained constant from morning to afternoon in controls, it increased in epilepsy. In contrast, oxidative phosphorylation increased in control and decreased in epilepsy. Thus, the control hippocampus shows circadian molecular remapping, which is altered in epilepsy. We suggest that the hippocampus operates in a different functioning mode in epilepsy. These alterations need to be considered when studying epilepsy mechanisms, designing drug treatments, and timing their delivery.

Commentary

In 1885, Sir Willian Richard Gowers, practicing neurologist at the National Hospital of the Paralyzed and Epileptics, reported that the seizures in many of his patients with epilepsy exhibited an intriguing day–night preference. He found that the seizures occurred almost exclusively at night in 21% of the 840 patients he studied and primarily by day in 43% of them.[1] Later reports confirmed and extended Gowers' findings to include a variety of different seizure preference patterns. Perhaps the most well-known example is that of catamenial epilepsy, where the seizures tend to occur at certain times during the menstrual cycle.[2] While physiological fluctuations in estrogen and progesterone are thought to underlie the undulating seizure vulnerability in catamenial epilepsy,[2] the mechanisms of other periodic seizure disorders are largely unknown.

Patients with mesial temporal lobe epilepsy (MTLE)—one of the commonest forms of medication-resistant epilepsy—also exhibit a striking 24-hour seizure periodicity with peak seizure vulnerability occurring in late afternoon, between 4 and 7 PM.[3] To search for possible seizure-driving chronomolecular factors in MTLE, Debski et al analyzed the hippocampal transcriptome and proteome in the pilocarpine mouse model of MTLE.[4] The analyses were performed on brain tissue samples from control and pilocarpine-treated mice collected at 6 different time points during the 24-hour ("circadian") cycle. The authors identified more than 1200 daily oscillating transcripts in normal mice versus 1600 in MTLE mice, with only one-fourth oscillating in both conditions. Moreover, several transcripts in the epilepsy mice exhibited phase changes and general increases in amplitude, as compared to controls, suggesting a different and more pronounced 24-hour gene periodicity in the epilepsy hippocampus.

For example, genes involved in aerobic glycolysis and oxidative phosphorylation exhibited different 24-hour expression patterns in control versus epilepsy brain. Aerobic glycolysis remained constant from morning to afternoon in controls but increased in epilepsy, and oxidative phosphorylation increased in controls and decreased in epilepsy. These are interesting findings because alterations in brain energy metabolism, specifically mitochondrial function,[5] lactate homeostasis,[6,7] and glucose utilization,[8] have been speculated to underlie the generation of spontaneous seizures in human MTLE. Thus, the results shed new light on the possible role of brain metabolic oscillations on seizure vulnerability in MTLE. Additionally, the study suggests that the time of day is likely to influence the results of metabolic imaging studies of animal models, and possibly also patients with epilepsy. However, whether the metabolic fluctuations throughout the day represent a sufficiently large bias to impact research and clinical decision-making based on metabolic brain imaging studies remains to be established.

The authors found that many other transcription products and proteins were expressed differently during the 24-hour

cycle in control versus epilepsy brains, including genes and proteins related to phosphorylation, protein folding, cell cycle, proteolysis, and chromosome organization. Notably, several core clock genes gained in oscillation amplitude in MTLE versus control, and the authors propose that the DNA binding regulator Runx1 plays a role in the exaggerated gene oscillations in MTLE. Runx1 interacts with two key histone deacetylases Hdac1 and Hdac2, which also show periodic activity, suggesting that epigenetic mechanisms are involved. The idea of epigenetic dysregulation in epilepsy is translationally important because pharmacological modulation of the epigenome is feasible, as evidenced by the several epigenetic modulators that are approved by the Food and Drug Administration for the treatment of hematological malignancies in humans.[9]

The authors also suggest that their results can be used for drug target design and chronotherapy. Using database searches and algorithms that detect rhythmicity in large-scale data sets, the authors discovered periodic oscillations in genes related to anti-seizure drug targets, drug carriers, drug enzymes, and drug transporters in normal and epilepsy brains. For example, new classes of anti-seizure drugs targeting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors are being developed, and many of the genes associated with these receptors showed differential expression patterns over the 24-hour cycle in epilepsy versus control brain. These findings suggest that the efficacy of many anti-seizure drugs varies across the 24-hour cycle and that knowledge about such variations can be used for more effective and tailored (ie, personalized) seizure chronotherapies.

In summary, Debski et al have demonstrated that the mouse hippocampus undergoes oscillations in numerous genes and proteins over the 24-hour day cycle and that many of these changes are unique to the epileptic hippocampus. The fact that the seizures in human MTLE and rodent models of the disease also exhibit undulating vulnerabilities across the 24-hour cycle, raises the intriguing possibility that the oscillations in brain molecules and seizures are mechanistically linked. For example, the molecular oscillations may be either a compensatory response to the seizures or a cause of them. However, the study does not resolve these issues nor does it drill into the molecular changes at the cellular level. While further research is needed to address these issues, it will also be interesting to know whether the rodent observations are translatable to human epilepsy and whether the findings can lead to more effective, personalized treatments of spontaneous seizures.

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