Epilepsy Currents
2021, Vol. 21(6) 447–448

DOI: 10.1177/15357597211043517
journals.sagepub.com/home/epi
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Brain Energy Oscillations–A Possible Explanation for Seizure Periodicity in Epilepsy?

Spatiotemporal heterogeneity in hippocampal metabolism in control and epilepsy conditions

Brancati GE, Rawas C, Ghestem A, Bernard C, and Ivanov AI. *Proc Natl Acad Sci USA*. 2021;118(11):e2013972118.

The hippocampus's dorsal and ventral parts are involved in different operative circuits, the functions of which vary in time during the night and day cycle. These functions are altered in epilepsy. Since energy production is tailored to function, we hypothesized that energy production would be space- and time-dependent in the hippocampus and that such an organizing principle would be modified in epilepsy. Using metabolic imaging and metabolite sensing ex vivo, we show that the ventral hippocampus favors aerobic glycolysis over oxidative phosphorylation as compared to the dorsal part in the morning in control mice. In the afternoon, aerobic glycolysis is decreased, and oxidative phosphorylation increased. In the dorsal hippocampus, the metabolic activity varies less between these two times but is weaker than in the ventral. Thus, the energy metabolism is different along the dorsoventral axis and changes as a function of time in control mice. In an experimental model of epilepsy, we find a large alteration of such spatiotemporal organization. In addition to a general hypometabolic state, the dorsoventral difference disappears in the morning, when seizure probability is low. In the afternoon, when seizure probability is high, the aerobic glycolysis is enhanced in both parts, the increase being stronger in the ventral area. We suggest that energy metabolism is tailored to the functions performed by brain networks, which vary over time. In pathological conditions, the alterations of these general rules may contribute to network dysfunctions.

Commentary

Mesial temporal lobe epilepsy (MTLE) is one of the commonest forms of medically refractory epilepsies and features spontaneous recurrent seizures that originate from mesial (anteromedial) temporal lobe structures, such as the hippocampus, the amygdala, and the entorhinal cortex. The seizures in MTLE have a remarkable tendency to occur more frequently during certain times of the day. In humans, the seizure frequency peaks in the late afternoon, between 16:00 and 19:00, and a smaller peak occurs in the morning, between 7:00 and 10:00[1]. Additionally, many animal models of MTLE exhibit a similar 24-hour ("circadian") seizure periodicity, albeit the number and timing of the peaks vary among the different models. It is interesting to note that some neocortical epilepsies also display periodicity, but that the timing of the peak depends on the location of the seizure focus. For example, occipital and parietal seizures occur in a strong Gaussian-like distribution, 180° out of phase relative to each other, with occipital seizures peaking between 16:00 and 19:00 and parietal seizures between 4:00 and 7:00.[1]

While the underlying mechanisms of seizure periodicity remain incompletely understood for most types of epilepsy, a recent proteomic and messenger ribonucleic acid (mRNA) sequencing study of the mouse pilocarpine model suggested that circadian oscillations in genes controlling brain energy metabolism may be linked to the periodicity in MTLE.[2] The authors reported that although aerobic glycolysis remained constant from morning to afternoon in controls, it increased in epilepsy. Moreover, oxidative phosphorylation increased in controls and decreased in epilepsy. It is well established that brain metabolism is altered at baseline in MTLE. The seizure focus is hypometabolic interictally[3] and exhibits changes in a variety of energy-related metabolites, enzymes, and reactive oxygen species.[4,5] Because normal synaptic transmission requires large amounts of energy to replenish ion gradients, and to clear (from the extracellular space), recycle, and synthesize new neurotransmitter, it has been speculated that energetic perturbations might be implicated in the triggering of seizures in MTLE.[6] Moreover, the fact that the ketogenic diet successfully prevents seizures in some epilepsies lends additional support to the idea that spontaneous seizures are linked to energy dysfunction.[7]

The current article by Brancati et al. takes a deeper dive into the fields of seizure periodicity and brain metabolism.[8] Because the anterior hippocampus (ventral hippocampus in rodents) is more prone to seizure activity than the posterior (dorsal) hippocampus,[9] the authors decided to compare aerobic glycolysis and oxidative phosphorylation between the two hippocampal regions at specific times of the day, in normal and pilocarpine-treated MTLE mice. Three hypotheses were tested: first, that energy production is different between the ventral and dorsal hippocampus under normal conditions; second, that any

dorsoventral organization of energy metabolism present in normal controls is altered in epilepsy; and third, that energy production varies as a function of time of the day. To this end, the authors used an incubated brain slice approach to measure aerobic glycolysis and oxidative metabolism at baseline and after electrical stimulation of the hippocampus. They compared ventral vs. dorsal slices, normal vs. epilepsy brains, and Zeitgeber 3 time (ZT3 – i.e.,, 3 hours of daylight) vs. Zeitgeber 8 time (ZT8 – i.e.,, 8 hours of daylight), which correspond to respectively low and high seizure probability in the pilocarpine model.

There were several notable findings. First, the ventral hippocampus favors aerobic glycolysis over oxidative metabolism as compared to the dorsal hippocampus in the morning in control mice. In the afternoon, aerobic glycolysis is decreased, and oxidative metabolism is increased. In the dorsal hippocampus, the metabolic activity varies less between the two times, but is weaker than in the ventral. Thus, the energy metabolism is different among the dorsoventral axis and changes as a function of time in control mice. Second, in epilepsy mice, there is a general hypometabolic state with disappearance of the dorsoventral difference in the morning when the seizure probability is low. In the afternoon, when seizure probability is high, the aerobic glycolysis is enhanced in both the dorsal and the ventral hippocampus, with the strongest enhancement being present in the ventral hippocampus.

These results suggest a potentially important link between enhanced aerobic glycolysis in the ventral hippocampus at certain times of the day, and increased vulnerability to seizures. The concept that aerobic glycolysis may be linked to seizures is not new, as the extracellular level of lactate (a possible marker of aerobic glycolysis) was found to be chronically elevated in the seizure focus in humans with medically refractory focal epilepsies of different types, including MTLE.[4] What is not clear, however, is whether aerobic glycolysis oscillates during the 24-hour cycle in the human epilepsy brain, and if such oscillations correlate with increased seizure vulnerability. Additionally, it is not known whether the metabolic changes observed in the pilocarpine-treated mice are a cause or a consequence of the seizures. Even though massive inhibition of brain energy production through the use of powerful toxins such as sodium fluoroacetate can trigger seizures,[10] it remains an open question whether more subtle metabolic oscillations may be a cause of spontaneous seizures and seizure periodicity in MTLE.

The potential clinical impact of this study is that carefully timed manipulations of brain energy metabolism may be used to suppress seizures more effectively than now. Brain energy metabolism is complex as it involves a network of substrates, enzymes, cofactors, and transporters; however, this complexity may be exploited therapeutically by pharmacological and/or dietary approaches that target specific nodes of this network. Thus, it is possible that treatments with selected metabolic substrates (e.g.,, the ketogenic diet and ketogenic amino acids) or pharmacological enhancers of oxidative metabolism during specific times of the day, will be quite effective (reviewed in[11]). However, to develop effective chronotherapeutic interventions, it is necessary to understand the causal relationship between the metabolic oscillations and seizures, and whether key components of the metabolic network can be manipulated in a safe and practical manner to effectively suppress seizures.

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