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Reconsidering Network Mechanisms in Absence Seizures: Unhitching the Wave Cart From the Spike Horse

Spike-Wave Discharges in Absence Epilepsy: Segregation of Electrographic Components Reveals Distinct Pathways of Seizure Activity

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Spike and wave discharges (SWDs) are the electrographic hallmark of absence seizures and the major diagnostic criterion for childhood absence epilepsy (CAE). In a widely accepted scheme, the alternating sequence of spikes and waves reflects an iterative progression of neuronal excitation during the spike component and post-excitatory silence during the wave component. Here, we challenge this view by showing that these two components are not necessarily coupled. In a genetic rat model of CAE, self-contained waves occurred in motor cortex in synchrony with SWDs in the somatosensory system during blockade of afferent input from the thalamus. Current source density analyses of multisite local field potentials (LFPs) revealed layer-specific activity, in which thalamic inputs induced a sequence of cellular-synaptic events underlying the spike component, while intracortical oscillations generated the wave component. These findings indicate novel principles of SWDs, where oscillatory cortical waves provide adequate time windows for integration of thalamocortical inputs and feedback responses during generation of seizure activity.

Commentary

Epilepsy is a brain network disorder associated with dysfunction of specific brain regions and the connectivity among them. Identification of seizure networks can help guide targets for network-selective neurostimulation therapies. Because brain stimulation is currently being evaluated for the treatment of generalized epilepsies,[1] it is critical to elucidate the generalized seizure networks.

The network physiology of one type of generalized seizure, absence seizures, and its EEG correlate, spike-wave complexes (SWCs), has been characterized in both animal models and human patients.[2] A simple model holds that increased neuronal firing in the deep layers of the primary somatosensory cortex (S1) coupled with feedforward and feedback interactions among S1 and the thalamic reticular (nRT) and ventrobasal (VB) nuclei produce synchrony and oscillatory neuronal burst firing associated the SWC rhythmic EEG spikes.

This simple model of SWC physiology is incomplete. First, while it accounts for the spike component of the SWC, it does not explain the formation of the characteristic waves. They are often presumed to be formed by hyperpolarization inextricably hitched to the preceding spike. Second, it does not incorporate the role of the centromedian nucleus (CM), the thalamic intralaminar nucleus currently targeted for neurostimulation in generalized epilepsy.[1] Finally, it does not explain the "pre-ictal" oscillations observed several seconds prior to the first SWC spike in several rodent models of absence seizures.[3-5]

In this article,[6] Terlau and colleagues tested the effects of selective pharmacological (DNQX) deactivation of VB and CM nuclei on SWCs recorded in S1 and secondary motor cortex (M2) in a rat strain that exhibits spontaneous absence seizures. They recorded S1 and M2 electrocorticograms (ECoG), transcortical LFPs, and multiunit activity (MUA). Current source density analyses of the LFPs revealed the time course of current entering ("sinks") and leaving ("sources") within the different cortical layers.

With ECoG recordings, the authors found that unilateral CM deactivation reduced SWC incidence at the S1/M2 sites by 44%/49%, values somewhat less than they achieved with VB deactivation (68%/54%). For the SWCs that persisted during VB inactivation, the voltage of both the wave and spike components was reduced at the S1 and M2 sites. In contrast, DNQX applied to CM reduced both spikes and wave voltages in S1 but decreased spike voltage in M2 without changing the waves. Moreover, in 9% of the M2 SWCs, there was no apparent spike component and only a "self-contained wave." These data demonstrated that spikes could be functionally decoupled ("unhitched") from the waves. Despite the disassociation of spikes from waves within M2, pairwise phase consistency measurements demonstrated that these

isolated waves behaved as SWCs and were not simply nonepileptic oscillatory activity.

In the absence of DNQX, the LFP recordings in S1 revealed a prominent spike-associated sink in layers II/III and IV and a prominent wave-associated sink in layer VI, results that qualitatively agreed with a previous study in another SWC rat model.[7] Additional S1 spike-associated sinks were identified in layers I and V. In M2 cortex, a region with minimal layer IV, a prominent spike-associated sink was identified in layer II/III with an additional region in layer I. A wave-associated sink was present in M2 layer V. In both S1 and M2, MUA was prominent in layers II to VI during the SWC spike component and markedly attenuated during the wave.

With CM deactivated by DNQX, LFPs recorded during the self-contained waves confirmed the initial assignment of the spike-associated sinks, both the layer II/III and layer I sinks were significantly reduced. Interestingly, the wave associated layer V sink was prolonged, a result that demonstrated that the cortical current flow produced during waves was not simply a consequence of a preceding spike.

Multiunit activity during the self-contained waves was significantly reduced compared to baseline. Interestingly, the paper's figures suggest that the remaining MUA was more prevalent during the first part of the self-contained wave, the time when the spike would have occurred, than during the latter half of the wave.

The first important result from this article is the finding that CM inactivation significantly reduced the incidence of SWCs. Although several previous investigators found that modulation of S1, nRT, and VB activity reduced SWCs, these brain regions have not been therapeutically targeted in human patients with drug-resistant generalized epilepsy. Conversely, while a few studies tested the effects of deactivating various midline thalamic nuclei on generalized seizures,[8,9] to my knowledge, the impact of selective deactivation of CM, the brain region targeted in previous and on-going human trials[1] has not been reported. Therefore, the current aprticle achieved an important milestone in quantifying the effects of CM neuromodulation in a well-established preclinical model of absence seizures.

Despite CM deactivation, residual SWCs were present and it is unknown if they resulted from incomplete CM blockade, activity of the contralateral CM, or, importantly, if CM contributes only a modulating and not an indispensable role in SWC generation. It would be important for future studies to record CM neuronal activity during DNQX application and test the effects of bilateral CM deactivation.

Previous reports demonstrated that on-demand electrical and optogenetic modulation of S1 or VB triggered by SWC detection (closed-loop modulation) effectively reduces SWCs in rodents.[10] In contrast, this article used an "open loop" method of CM neuromodulation; DNQX was infused continuously for tens of minutes and not "on-demand" in response to detected SWCs. Therefore, it is unknown if CM inhibition could abort a SWC or simply acts to reduce the probability of its formation. Consequently, it is necessary for future studies to test the effects of closed-loop CM neuromodulation on generalized seizures.

Additional key findings in this article are that SWC waves can be selectively decoupled from spikes, and importantly, spikes and waves exhibit distinct spatial–temporal patterns of cortical current flow. Waves are not simply a result of rebound hyperpolarization that is inextricably hitched to the preceding spike. Current source density analysis localized the wave-associated sinks to M2 layer V, a layer in which pyramidal neurons are directly innervated by S1 layer V/VI neurons. Therefore, the authors suggest that waves are generated by intracortical oscillations involving S1 deep layer neurons. Future studies that genetically target and selectively inhibit cortical neurons projecting to M2 layer V can test this hypothesis.

Terlau and colleagues discuss 2 interesting implications for their finding of self-contained, intracortically generated waves. First, the wave may create a time window for the gating of thalamocortical and corticothalamic signaling and thus generate a synchronous response (eg, waves may evoke synchronized hyperpolarization-activated currents in the target neurons thus allowing them to fire together in response to thalamocortical input). Future studies that perform intracellular recordings of the M2 neurons during the self-contained waves can determine the effects of the waves on intrinsic excitability. Second, the authors suggest that the intracortical waves may be related to the "pre-ictal" oscillations that can be detected seconds prior to the initial SWC spike.[3-5] Identification of these oscillations has been instrumental in demonstrating that absence seizures do not arise instantaneously from a baseline background but develop in the setting of a pre-ictal oscillatory state. However, unlike the wave component of SWCs, the pre-ictal waves are much less periodic or prominent and are typically identified using quantitative signal analysis measures. It would be interesting for future studies to use these quantitative techniques to identify pre-ictal oscillations and determine whether they have similar sinks and sources as the self-contained waves identified here.

In conclusion, by pharmacologically unhitching SWC spike and wave components, this article extends our understanding of the basic neurophysiology of absence seizures and provides important, clinically translatable data applicable to trials of CM neurostimulation. It will be important for follow-up studies to determine the ability of open- and closed-loop CM inactivation to more effectively inhibit SWCs and to elucidate the effects of waves on the intrinsic physiology of cortical neurons.

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