Epilepsy Currents
2024, Vol. 24(2) 129-131
© The Author(s) 2024
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15357597241228466
journals.sagepub.com/home/epi
Sage

Lost in the Woods: Spatially Miscomputing Dendritic Trees

Targeting Aberrant Dendritic Integration to Treat Cognitive Comorbidities of Epilepsy

Masala N, Pofahl M, Haubrich AN, Islam KUS, Nikbakht N, Pasdarnavab M, Bohmbach K, Araki K, Kamali F, Henneberger C, Golcuk K, Ewell LA, Blaess S, Kelly T, Beck H. *Brain*. 2023;146(6):2399-2417. doi:10.1093/brain/awac455

Memory deficits are a debilitating symptom of epilepsy, but little is known about mechanisms underlying cognitive deficits. Here, we describe a Na+ channel-dependent mechanism underlying altered hippocampal dendritic integration, degraded place coding and deficits in spatial memory. Two-photon glutamate uncaging experiments revealed a marked increase in the fraction of hippocampal first-order CA1 pyramidal cell dendrites capable of generating dendritic spikes in the kainate model of chronic epilepsy. Moreover, in epileptic mice dendritic spikes were generated with lower input synchrony, and with a lower threshold. The Nav1.3/1.1 selective Na+ channel blocker ICA-121431 reversed dendritic hyperexcitability in epileptic mice, while the Nav1.2/1.6 preferring anticonvulsant S-Lic did not. We used in vivo two-photon imaging to determine if aberrant dendritic excitability is associated with altered place-related firing of CA1 neurons. We show that ICA-121431 improves degraded hippocampal spatial representations in epileptic mice. Finally, behavioural experiments show that reversing aberrant dendritic excitability with ICA-121431 reverses hippocampal memory deficits. Thus, a dendritic channelopathy may underlie cognitive deficits in epilepsy and targeting it pharmacologically may constitute a new avenue to enhance cognition.

Commentary

In human epileptic patients and animal models of epilepsy there are numerous cognitive comorbidities associated with learning and memory.[1-3] In rodents, the kainic acid model of mesial temporal lobe epilepsy produces long-term performance deficits in navigation and behavioral tasks that depend on spatial memory.[4,5] Perhaps the most directly measurable, neurophysiological readout of spatial representations in the rodent brain come in the form of "place cells," hippocampal neurons which fire preferentially when the mouse is in a particular spatial location (e.g., along a track of a maze).[6] Notably, place cell firing is disrupted in epileptic animals, with CA1 place cells having aberrant phase procession and being significantly unstable over the course of 1 week.[7,8]

There is mounting evidence that sharply tuned place cells emerge as a result of dendritic computation that amplifies synchronous glutamatergic synaptic input.[9] This type of dendritic nonlinear amplification of synchronous input has been shown to arise, at least in part, from sodium spikes initiating when dendrites of pyramidal cells cross a voltage threshold.[10] As with many ion channels, sodium channels are significantly dysregulated in animal models of epilepsy.[11]

In the highlighted study,[12] Masala et al seek to test a hypothesis that unifies the above observations that aberrant sodium channel expression in epileptic mice leads to pathological dendritic spike initiation, which in turn disrupts place cells and consequently impairs spatial navigation. While there is support in the literature for each premise of this hypothesis, the authors designed experiments to validate each of these findings and to test the overarching hypothesis that dendritic sodium channels are causally linked to spatial navigation deficits in epileptic animals. The authors systematically test this hypothesis using a series of advanced experimental techniques that characterize differences between control mice and mice with spontaneous recurrent seizures resulting from intracortical kainate injection. First, they provide 5 lines of evidence that CA1 pyramidal cells in hippocampal slices from epileptic animals have a higher propensity for generating dendritic spikes: (1) unitary EPSPs induced by photo-uncaging glutamate quasi-simultaneously at multiple dendritic spines sum with a higher-than-expected gain and higher probability of supralinear summation (dendritic spikes) in first order dendrites of epileptic animals, (2) dendritic spike threshold is lower in epileptic animals, (3) the slope of rising edge of dendritic spike is higher in epileptic mice (slow phase of summed EPSP was not different), (4) in epileptic mice, dendritic spikes were generated even with decreased synchrony of synaptic input (while control mouse dendritic spikes dropped off quickly with synchrony),

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

and (5) spike generation inactivation was significantly less in epileptic mice. Next, they demonstrated the role of sodium channels in aberrant dendritic spiking by showing that altered dendritic summation of unitary EPSPs in epileptic mice was normalized by the broad spectrum voltage-gated sodium channel blocker tetrodotoxin or selective blockade of $Na_v1.3$ and $Na_v1.1$ with ICA-121431, but not by selective blocker of $Na_v1.2$ and $Na_v1.6$, S-lic. The effect of ICA-121431 appeared to be selective for dendritic sodium channels as it had no effect on somatic action potentials. Finally, in correlating these electrophysiological effects with molecular changes in sodium channels, they found that $Na_v1.3$ expression was dysregulated in epileptic animals, as demonstrated by an increase in Scn3a microRNA (mRNA) and Nav1.3 protein in pyramidal cells and a decrease in Scn3a mRNA in interneurons.

In attempting to link these dendritic sodium channel defects to cognitive dysfunction, in vivo experiments probed the spatial navigation deficits in epileptic mice. The primary findings were that, as previously demonstrated, place fields were significantly less precise in epileptic mice, but that ICA-121431 restored place field precision to the level of control mice. Finally, to evaluate whether the effects of ICA-121431 had behaviorally relevant implications, the authors performed 3 behavioral spatial learning assays. In 2 of the 3 tests epileptic animals performed poorer. ICA-124131 rescued performance in the task that required hippocampal-dependent memory consolidation but not in the task depending solely on spatial working memory.

Interestingly, although previous work has shown that interictal spikes disrupt place cell performance,[13] ICA-121431 did not affect interictal spike duration or frequency, suggesting it acts independently of interictal spikes. In this model of epilepsy, as with the similar intrahippocampal kainate model, there is a lot of aberrant nonconvulsive neuronal activity observed: >10 discharges per minute, ranging from 0 to >5 seconds in duration, none of which were affected by ICA-121431. This detail is surprising in that frequent synchronous events do not disrupt spike-coding in a sparsely firing population of pyramidal cells and in that a voltage-gated sodium channel blocker does not affect such activity.

The subtlety of the effect of $Na_v1.3/1.1$ blockade, combined with the gene expression characterization and optical probing of dendritic excitability, is strong evidence that the highlighted study is zeroing in on a specific mechanism of epilepsy-related spatial memory deficits. However, the only evidence demonstrating that $Na_v1.3/1.1$ sodium channels are *causally* linked to the behavioral comorbidities described depends on pharmacological agents which may have off-target effects. Perhaps future studies will further test the hypothesized mechanism using a nonepileptic positive control. For example, does overexpression of $Na_v1.3$ (e.g., using an AAV vector) lead to similar pathophysiology in dendritic spiking and spatial memory? Specific genetic knockdowns (e.g., with mRNA) may help to further isolate the role of $Na_v1.3$ versus that of $Na_v1.1$. Such genetic manipulations enable the dissection of not only specific sodium channel subtypes that are involved but also in which cell types they are creating relevant pathology by selectively overexpressing or knocking down $Na_v1.3$ in pyramidal cells versus interneurons.

It will be interesting to see how generalizable the findings of the highlighted study are. For example, it will be important to test whether ICA-121431 rescues spatial memory deficits observed in other mouse models of epilepsy such as pilocarpine or systemic kainate. Beyond the field of epilepsy are well-established spatial memory deficits in other neurological diseases such as Alzheimer's disease (AD) and Parkinson's disease related to increased propensity for dendritic spiking caused by dysregulation of $Na_v1.3$ and $Na_v1.1$? A mouse model of AD shows a shift in the balance of sodium channel subunits,[14] although it is unclear whether the findings align with those of Masala et al, as the transcriptomics and proteomics were confined to $Na_v1.3$ and $Na_v1.2$ in the highlighted study, whereas the AD study identified dysregulation of $Na_v1.1$ channels. A rat model of Parkinson's Disease, which also has spatial memory deficits, did exhibit comparable overexpression of $Na_v1.3$.[15]

It is always challenging to connect the actions of a single ion channel to a behavioral output. However, in the highlighted work, Masala and colleagues provide broad evidence for such a link between dysregulation of $Na_v1.3$, aberrant dendritic spiking, and spatial memory dysfunction. If future studies reveal this to be a robust and generalizable link, there may be a relatively straightforward path to a highly specific treatment for a significant comorbidity of epilepsy and potentially other neurological conditions.

Kyle P. Lillis, PhD
Department of Neurology,
Massachusetts General Hospital,
Harvard Medical School

ORCID iD

Kyle P. Lillis http://orcid.org/0000-0003-0219-8113

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Reyes A, Holden HM, Chang YHA. Impaired spatial pattern separation performance in temporal lobe epilepsy is associated with visuospatial memory deficits and hippocampal volume loss. *Neuropsychologia*. 2018;111:209-215. doi:10.1016/j.neuropsychologia.2018.02.009.
2. Löscher W, Stafstrom CE. Epilepsy and its neurobehavioral comorbidities: insights gained from animal models. *Epilepsia*. 2023;64(1):54-91. doi:10.1111/epi.17433
3. Abrahams S, Morris RG, Polkey CE. Hippocampal involvement in spatial and working memory: a structural MRI analysis of patients with unilateral mesial temporal lobe sclerosis. *Brain Cogn*. 1999;41(1):39-65. doi:10.1006/brcg.1999.1095

4. Gayoso MJ, Primo C, Al-Majdalawi A, Fernandez JM, Garrosa M, Iñiguez C. Brain lesions and water-maze learning deficits after systemic administration of kainic acid to adult rats. *Brain Res*. 1994;653(1-2):92-100. doi:10.1016/0006-8993(94)90376-x
5. Sarkisian MR, Tandon P, Liu Z, et al. Multiple kainic acid seizures in the immature and adult brain: ictal manifestations and long-term effects on learning and memory. *Epilepsia*. 1997; 38(11):1157-1166. doi:10.1111/j.1528-1157.1997.tb01211.x
6. O'Keefe J, Nadel L. *The Hippocampus as a Cognitive Map*. Oxford University Press; 1978. Accessed December 5, 2023. http://www.cognitivemap.net/
7. Lenck-Santini PP, Holmes GL. Altered phase precession and compression of temporal sequences by place cells in epileptic rats. *J Neurosci*. 2008;28(19):5053-5062. doi:10.1523/JNEUROSCI.5024-07.2008
8. Shuman T, Aharoni D, Cai DJ, et al. Breakdown of spatial coding and interneuron synchronization in epileptic mice. *Nat Neurosci*. 2020;23(2):229-238. doi:10.1038/s41593-019-0559-0
9. Basak R, Narayanan R. Spatially dispersed synapses yield sharply-tuned place cell responses through dendritic spike initiation. *J Physiol*. 2018;596(17):4173-4205. doi:10.1113/JP275310
10. Golding NL, Spruston N. Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons. *Neuron*. 1998;21(5):1189-1200. doi:10.1016/S0896-6273(00)80635-2
11. Royeck M, Kelly T, Opitz T, et al. Downregulation of spermine augments dendritic persistent sodium currents and synaptic integration after status epilepticus. *J Neurosci*. 2015;35(46): 15240-15253. doi:10.1523/JNEUROSCI.0493-15.2015
12. Masala N, Pofahl M, Haubrich AN, et al. Targeting aberrant dendritic integration to treat cognitive comorbidities of epilepsy. *Brain*. 2022;146(6):2399-2417. doi:10.1093/brain/awac455
13. Zhou JL, Lenck-Santini PP, Zhao Q, Holmes GL. Effect of interictal spikes on single-cell firing patterns in the hippocampus. *Epilepsia*. 2007;48(4):720-731. doi:10.1111/j.1528-1167.2006.00972.x
14. Verret L, Mann EO, Hang GB, et al. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. *Cell*. 2012;149(3):708-721. doi:10.1016/j.cell.2012.02.046
15. Wang Z, Lin Y, Liu W, et al. Voltage-gated sodium channels are involved in cognitive impairments in Parkinson's disease—like rats. *Neuroscience*. 2019;418:231-243. doi:10.1016/j.neuroscience.2019.08.024