Published in final edited form as:

Neurosci Lett. 2011 June 27; 497(3): 247–250. doi:10.1016/j.neulet.2011.03.070.

Interictal spikes: harbingers or causes of epilepsy?

Kevin J Staley, MD¹, Andrew White, MD PhD², and F Edward Dudek, PhD³

Kevin J Staley: kstaley@partners.org; Andrew White: white.andrew@tchden.org; F Edward Dudek: ed.dudek@hsc.utah.edu

¹ Department of Neurology, Massachusetts General Hospital, 55 Fruit St, WAC 708-D, Boston, MA 02114

² Departments of Pediatrics and Neurology, School of Medicine, University of Colorado Health Sciences Campus, Denver, CO 80262

³ Department of Physiology, University of Utah School of Medicine, 420 Chipeta Way, Suite 1700, Salt Lake City, UT 84108-1256, USA

Abstract

Interictal spikes are brief paroxysmal electrographic discharges observed between spontaneous recurrent seizures in epileptic patients. The relationship between interictal spikes and the seizures that define acquired epilepsy has been debated for decades. Recent studies using long-term continuous electrographic recordings from the hippocampus and cortex in rats with kainate-induced epilepsy suggest that electrographic spikes, with waveforms similar to interictal spikes, precede the occurrence of the first spontaneous epileptic seizure. These data raise the possibility that spikes might serve as a surrogate marker of ongoing chronic epileptogenesis. Additionally, electrographic spikes might actually contribute to the development and maintenance of the epileptic state (i.e. the increased probability of spontaneous recurrent seizures). Correlational evidence for such a causal relationship has recently also been obtained in an in vitro model of epileptogenesis using organotypic hippocampal slices. Testing for a causal relationship will ultimately require selective anti-spike medications. Although no such agents currently exist, this new preparation is amenable to moderate-throughput screening, which should accelerate their discovery. Anti-spike agents may also be of benefit in ameliorating the cognitive dysfunctions associated with epilepsy, to which spike activity may contribute.

Introduction

The title of this article will probably raise some questions. Interictal spikes are brief paroxysmal discharges of <250 ms duration that can be observed on either the scalp or cortical electroencephalogram (EEG). These electrographic spikes arise from the synchronous activation of neurons in the underlying cortex [31], and may influence distributed cortical networks [16], transiently interfering with cognition [19]. But, what about the word “interictal” in the title? Interictal means “between seizures,” so “interictal spikes” refers to electrographic spikes that occur between seizures. Epileptogenesis is the process by which the brain becomes prone to spontaneous seizures. By the time seizures

© 2011 Published by Elsevier Ireland Ltd.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

occur, epileptogenesis would seem to be over. Thus, by the time interictal spikes appear, isn't the opportunity to interfere with epileptogenesis over?

There are two important approaches to answering this question. The first is detailed in the accompanying paper by Dudek et al., describing epileptogenesis as a continuously progressive process that does not stop or even diminish after the first spontaneous seizure [13]. Progression of temporal lobe epilepsy has been suspected based on both clinical measures, such as increased seizure frequency and sequentially poorer responses to anticonvulsant therapies [23], as well as progressive grey matter volume loss evident on serial MRI scans [4;5]. Epileptogenesis is difficult to study in humans because of the heterogeneity of epileptogenic injuries, a latent period lasting months to decades [1], and the potentially confounding effects of anticonvulsant treatment after the first spontaneous seizures. Anticonvulsants have a poor track record as antiepileptogenic treatments [32], so anticonvulsant treatment would not be expected to alter the natural history of epilepsy; nonetheless, anticonvulsant therapy often alters seizure probability and thereby affects measures of epilepsy severity. Animal models of epileptogenesis overcome many of these difficulties and have provided a picture of epileptogenesis as a process that begins at the time of injury and progresses in severity well after the first spontaneous seizures occur [35]. In this context, antiepileptogenic treatment may be useful after the first seizure in order to prevent the worsening of epilepsy.

The second way to address the utility of treating interictal spikes as an antiepileptogenic target is to ask whether the term "interictal" is always appropriate to describe electrographic spikes. The terminology arose from the clinical pattern of referral to EEG laboratories: patients thought to have had a seizure are routinely referred to the EEG laboratory, and the presence of spikes is often associated with epilepsy; however, patients without seizures are rarely examined for the presence of electrographic spikes [36]. Why don't we look for spikes in brain-injured patients prior to the onset of spontaneous seizures?

Human studies of electrographic precursors to posttraumatic epilepsy

In the days of paper EEG records, prolonged recordings were rare and spike counting was a heroic task performed by hand without the benefit of computerized signal analysis and detection algorithms available today. Thus, most early studies of posttraumatic epilepsy lumped spikes and slowing together and asked if any EEG abnormality predicted posttraumatic epilepsy. Early reports suggested that the EEG was of predictive utility [25]. However, the death knell for EEG prediction of epilepsy was sounded by an influential paper published in 1975 by Jennett and van de Sande [18]. This was a brief retrospective study of routine EEG records in a population of 722 patients in whom the incidence of posttraumatic epilepsy was 43%. It is not made clear in this brief report whether the authors reviewed the EEGs recordings or (as is stated for controls) or only the EEG reports. The authors lumped EEG abnormalities of any kind together, and found that "any EEG abnormality" (whether focal or diffuse, epileptiform or not) was not predictive of posttraumatic epilepsy. The nature of the abnormal EEG patterns, the frequencies of the different abnormalities, and the correlations of individual EEG abnormalities to later epilepsy were not described in the report. However, the authors did acknowledge that more prolonged studies and more detailed analyses might have been helpful, and that in earlier studies the presence of interictal spikes appeared to be a more specific marker for future epilepsy [9]. From this widely cited study, it was concluded that the EEG was of no predictive value for posttraumatic epilepsy, and investigations were discontinued. In the modern era of digital EEG, multi-day recordings, and algorithms for automated spike detection, it would seem that the predictive value of interictal spikes could be addressed more conclusively than was possible in the time of Jennett and van de Sande [18].

Experimental studies of electrographic precursors to chronic epilepsy

Limitations of the Jennett and van de Sande study include use of nonspecific predictors (i.e., any EEG abnormality), short EEG samples that may have missed infrequent epileptiform activity, and a relatively short follow-up period in the population of patients that did not develop epilepsy (i.e., inadequate time to ascertain unequivocally that these patients did not later develop epilepsy). Shortcomings such as incomplete follow-up are difficult and expensive to address clinically, but can readily be addressed in experimental paradigms in which epileptogenesis is accelerated, increasing the feasibility of intensive EEG monitoring and analysis. We recently characterized epileptogenesis after low- and high-dose kainic acid injury in rats, using continuous radiotelemetric electrographic monitoring for 3 months after kainate-induced status epilepticus with automated spike and seizure detection to characterize the onset of epileptiform activity as a function of time [34]. A key finding in this long-term monitoring study was the emergence of “interictal” spikes prior to spontaneous seizure activity (Fig. 1 and 2). Quantification of the spike activity produced predictors of the development of subsequent epilepsy. These predictors included the amount of spike activity over periods of at least 24 hours and the development of clusters of spikes (epochs of regular spiking at 0.15–0.6 Hz that lasted for minutes to hours). Because the rats received either high- or low-dose kainate and none of the rats in the low-dose group developed epilepsy after status epilepticus, other powerful predictors of epilepsy in this study were the dose of kainate and duration of status epilepticus. Thus, these findings regarding EEG predictors of epilepsy need verification in additional prospective studies using other seizure models and a broader distribution of epileptogenic injuries.

The predictive utility of interictal spikes was recently tested in a febrile seizure model [12] using intermittent video EEG recording and manual spike and seizure detection. Importantly, the findings included the development of spikes before seizures in all animals that became epileptic, confirming the idea that spikes develop prior to spontaneous seizures in animal models of epileptogenesis. However, spikes also developed in rats in which seizures were never identified; the authors speculate that this could be a consequence of failure to identify spontaneous seizures in these rats. Intermittent EEG recording, combined with manual spike and seizure identification, is often the most feasible experimental method, but this approach makes seizures more likely to be missed in studies of epileptogenesis.

Compared to human epilepsy, animal models of epileptogenesis dramatically reduce the time to develop intractable epilepsy. However as the febrile seizure experience demonstrates, even a period of months represents a substantial feasibility challenge due to the amount of electrographic data that must be recorded and analyzed. Seizure activity has been reported in organotypic hippocampal brain slices after weeks in culture [21]. We recently characterized this seizure activity and found that rodent organotypic hippocampal brain slices represent a robust model of epileptogenesis with a substantially compressed time course [14] compared to in vivo models of epilepsy. This in vitro model clearly has no blood-brain barrier or immune system, yet epileptiform activity in the slice cultures exhibits the same temporal pattern of “spikes before onset of the first spontaneous seizure” observed in vivo. Interictal spikes developed at 7–10 days in culture, followed by seizures later in the second week, and episodes of status epilepticus during the third week in culture; and, by 4–6 weeks in culture, the slices exhibited brief, regular discharges that resembled periodic lateralized epileptiform discharges seen in severe human epilepsies, such as *epilepsia partialis continua* [3]. Seizure activity, but not interictal spikes in this preparation, responds to anticonvulsants such as phenytoin at clinically relevant concentrations. This preparation provides additional evidence for the early appearance of spikes during epileptogenesis. Organotypic slices represent a tractable model for studying the pathophysiological role of spikes in epileptogenesis and for developing therapies directed at preventing spikes.

What is the role of spikes in epileptogenesis?

Anti-spike therapies would only be useful if spikes are an important component of the pathogenesis of epilepsy [29]. The correlation of spikes and epilepsy has long been recognized and forms the basis for the diagnostic use of the electroencephalogram. Studies of temporal lobe epilepsy [24] and seizure surgery [7;20;22] support the prognostic significance of spikes and spike frequency in human epilepsy. Such correlations suggest that spikes may be influencing the natural history of epilepsy. Experimental studies demonstrate that in some developmental systems, spikes are necessary to guide axon sprouting [6]. We have postulated that after loss of interneurons, the consequent disinhibition is sufficient to induce spikes, and these spikes may lead newly sprouting axon terminals to form recurrent excitatory connections with other neurons in the same network [28]. This process, a recapitulation of the developmental “fire together, wire together” theme, could create the epileptic focus that subsequently initiates spontaneous seizures. However, it has also been proposed that the pathophysiological role of interictal spikes is simply to transiently reduce the probability of other epileptiform discharges [11]. While we concur with the idea that spikes induce a transient refractoriness in the epileptic network [27;30], the synchronous synaptic activation and membrane depolarization that occur during spikes also satisfy the requirements for induction of long-term increases of the strength of neurons in the epileptic focus [2], a process that should increase the probability of seizures.

Anti-spike therapeutic possibilities

Selective suppression of interictal spike activity would comprise an “acid test” of the hypothesis that interictal spikes are an important component of epileptogenesis. Currently, such therapy does not exist, and only benzodiazepine agents have been demonstrated to suppress spike activity [10;26]. In vitro models of interictal spikes, such as the disinhibited acute CA3 slice preparation [33], provide a potentially rapid screening paradigm. We have found imperfect pharmacological correlations between the synaptic physiology of the acute in vitro slice preparation [2] and in vivo models of epilepsy [17], though these may represent real differences in synaptic plasticity in vitro vs. in vivo [8]. We are currently exploring the feasibility of using the organotypic slice preparation as a platform for screening anti-spike and antiepileptogenic agents, using the more realistic but labor intensive in vivo models of chronic epilepsy as a second-stage screen. Spikes influence widespread cortical networks, and evidence is accumulating that spiking interferes with normal cognition [15;19]. Thus, independent of effects on epileptogenesis, anti-spike agents may be of utility in reducing cognitive comorbidity in epilepsy caused by interictal activity.

Summary and conclusions

Interictal spikes have been detected prior to spontaneous seizures in experimental epileptogenesis. Although studies in the days of pen-and-ink EEG recordings did not find a robust predictive relationship between spikes and the development of epilepsy, this question clearly needs to be readdressed using longer samples, modern digital recordings, and computational spike detection technology. Interictal spikes may play an important role in the pathogenesis of epilepsy, and may prove to be valuable biomarkers of this disease. It is even possible that future clinical efforts will be directed at the early detection and suppression of spikes in order to modify epileptogenesis.

Reference List

1. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. *N Engl J Med.* 1998; 338:20–24. [PubMed: 9414327]

2. Bains JS, Longacher JM, Staley KJ. Reciprocal interactions between CA3 network activity and strength of recurrent collateral synapses. *Nat Neurosci.* 1999; 2:720–726. [PubMed: 10412061]
3. Baykan B, Kinay D, Gokyigit A, Gurses C. Periodic lateralized epileptiform discharges: association with seizures. *Seizure.* 2000; 9:402–406. [PubMed: 10985996]
4. Bernhardt BC, Worsley KJ, Kim H, Evans AC, Bernasconi A, Bernasconi N. Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy. *Neurology.* 2009; 72:1747–1754. [PubMed: 19246420]
5. Bonilha L, Rorden C, Appenzeller S, Coan AC, Cendes F, Li LM. Gray matter atrophy associated with duration of temporal lobe epilepsy. *Neuroimage.* 2006; 32:1070–1079. [PubMed: 16872843]
6. Carmichael ST, Chesselet MF. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *J Neurosci.* 2002; 22:6062–6070. [PubMed: 12122067]
7. Cascino GD, Kelly PJ, Sharbrough FW, Hulihan JF, Hirschorn KA, Trenerry MR. Long-term follow-up of stereotactic lesionectomy in partial epilepsy: predictive factors and electroencephalographic results. *Epilepsia.* 1992; 33:639–644. [PubMed: 1628577]
8. Clem RL, Celikel T, Barth AL. Ongoing in vivo experience triggers synaptic metaplasticity in the neocortex. *Science.* 2008; 319:101–104. [PubMed: 18174444]
9. Courjon JA. The late effects of head injury. In: Walker, AE.; Caveness, WF.; Critchley, M., editors. *Posttraumatic Epilepsy in Electroclinical Practice.* Charles C. Thomas; Springfield: 1969. p. 215–227.
10. Dahlin M, Knutsson E, Amark P, Nergardh A. Reduction of epileptiform activity in response to low-dose clonazepam in children with epilepsy: a randomized double-blind study. *Epilepsia.* 2000; 41:308–315. [PubMed: 10714402]
11. de CM, Avanzini G. Interictal spikes in focal epileptogenesis. *Prog Neurobiol.* 2001; 63:541–567. [PubMed: 11164621]
12. Dube CM, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, Andres AL, Nalcioğlu O, Obenaus A, Vezzani A, Baram TZ. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. *J Neurosci.* 2010; 30:7484–7494. [PubMed: 20519523]
13. Dudek FE, Staley KJ. Early markers of epileptogenesis following injury: Implications for therapy. 2010; (This)
14. Dyhrfjeld-Johnsen J, Berdichevsky Y, Swiercz W, Sabolek H, Staley KJ. Interictal spikes precede ictal discharges in an organotypic hippocampal slice culture model of epileptogenesis. *J Clin Neurophysiol.* 2010 in press.
15. Galanopoulou AS, Moshe SL. The epileptic hypothesis: developmentally related arguments based on animal models. *Epilepsia.* 2009; 50(Suppl 7):37–42. [PubMed: 19682049]
16. Gotman J. Epileptic networks studied with EEG-fMRI. *Epilepsia.* 2008; 49(Suppl 3):42–51. [PubMed: 18304255]
17. Hellier JL, White A, Williams PA, Edward DF, Staley KJ. NMDA receptor-mediated long-term alterations in epileptiform activity in experimental chronic epilepsy. *Neuropharmacology.* 2009; 56:414–421. [PubMed: 18930747]
18. Jennett B, Van De Sande J. EEG prediction of post-traumatic epilepsy. *Epilepsia.* 1975; 16:251–256. [PubMed: 807472]
19. Kleen JK, Scott RC, Holmes GL, Lenck-Santini PP. Hippocampal interictal spikes disrupt cognition in rats. *Ann Neurol.* 2010; 67:250–257. [PubMed: 20225290]
20. Krendl R, Lurger S, Baumgartner C. Absolute spike frequency predicts surgical outcome in TLE with unilateral hippocampal atrophy. *Neurology.* 2008; 71:413–418. [PubMed: 18614768]
21. McBain CJ, Boden P, Hill RG. Rat hippocampal slices ‘in vitro’ display spontaneous epileptiform activity following long-term organotypic culture. *J Neurosci Methods.* 1989; 27:35–49. [PubMed: 2563782]
22. Miller JW, Gotman J. The meaning of interictal spikes in temporal lobe epilepsy: should we count them? *Neurology.* 2008; 71:392–393. [PubMed: 18678822]
23. Pitkanen A, Sutula TP. Is epilepsy a progressive disorder? Prospects for new therapeutic approaches in temporal-lobe epilepsy. *Lancet Neurol.* 2002; 1:173–181. [PubMed: 12849486]

24. Rosati A, Aghakhani Y, Bernasconi A, Olivier A, Andermann F, Gotman J, Dubeau F. Intractable temporal lobe epilepsy with rare spikes is less severe than with frequent spikes. *Neurology*. 2003; 60:1290–1295. [PubMed: 12707431]
25. Roseman E, Woodhall B. *Res Publs Ass Res nerv ment Dis*. 1946; 25:200–219.
26. Sharief MK, Sander JW, Shorvon SD. The effect of oral flumazenil on interictal epileptic activity: results of a double-blind, placebo-controlled study. *Epilepsy Res*. 1993; 15:53–60. [PubMed: 8325278]
27. Staley KJ, Bains JS, Yee A, Hellier J, Longacher JM. Statistical model relating CA3 burst probability to recovery from burst-induced depression at recurrent collateral synapses. *J Neurophysiol*. 2001; 86:2736–2747. [PubMed: 11731533]
28. Staley KJ, Dudek FE. Role of interictal spikes in epileptogenesis. *Neuroscientist*. 2005; 11:272–276. [PubMed: 16061513]
29. Staley KJ, Dudek FE. Interictal spikes and epileptogenesis. *Epilepsy Currents*. 2006; 6:199–202. [PubMed: 17260059]
30. Staley KJ, Longacher M, Bains JS. Presynaptic modulation of CA3 network activity. *Nat Neurosci*. 1998; 1:201–209. [PubMed: 10195144]
31. Tao JX, Baldwin M, Hawes-Ebersole S, Ebersole JS. Cortical substrates of scalp EEG epileptiform discharges. *J Clin Neurophysiol*. 2007; 24:96–100. [PubMed: 17414965]
32. Temkin NR. Preventing and treating posttraumatic seizures: the human experience. *Epilepsia*. 2009; 50(Suppl 2):10–13. [PubMed: 19187289]
33. Traub, RD.; Miles, R. *Neuronal networks of the hippocampus*. Cambridge University Press; New York: 1991.
34. White A, Williams PA, Hellier JL, Clark S, Edward DF, Staley KJ. EEG spike activity precedes epilepsy after kainate-induced status epilepticus. *Epilepsia*. 2009
35. Williams PA, White AM, Clark S, Ferraro DJ, Swiercz W, Staley KJ, Dudek FE. Development of spontaneous recurrent seizures after kainate-induced status epilepticus. *J Neurosci*. 2009; 29:2103–2112. [PubMed: 19228963]
36. Zivin L, Marsan CA. Incidence and prognostic significance of “epileptiform” activity in the eeg of non-epileptic subjects. *Brain*. 1968; 91:751–778. [PubMed: 5704833]

Figure 1.

Time course of electrographic spikes and seizures in rats after convulsive status epilepticus induced by kainate [34]. Times given in the figure represent ranges for the duration of each interval. The top timeline describes spike observations. High-frequency epileptiform discharges (HFED) (i.e. spiking) occurred shortly after status epilepticus; subsequently, the spikes gradually decreased in frequency (low-frequency epileptiform discharges, LFED). Individual spikes and spike clusters persisted for the life of the animal. The lower timeline describes the time course of seizure activity. Convulsive seizures appeared during kainate treatment, and then disappeared within 24 h (bottom timeline). After a seizure-free interval, seizures occurred again, but initially at a low frequency. Seizure activity increased slowly and then increased more rapidly, after which it often began to show a plateau. In all rats with convulsive status epilepticus ($n=9$), spike clusters occurred prior to the end of the seizure-free interval. The transition phase was defined as the time from the first kainate treatment until 10 seizures were observed per day for 2 consecutive days.

Figure 2.

The time course of spikes and spontaneous recurrent seizures following after kainate-induced status epilepticus. (A) The frequency of interictal spikes and seizures after kainate treatment. Data are shown as mean normalized frequencies of spikes or seizures versus time since kainate treatment, which has been normalized to the time of maximum seizure frequency. The data were normalized in order to illustrate that the frequency of interictal spikes was high and increased before seizure frequency began to increase, and the increase in spike versus seizure frequency was independent of the time course of seizure frequency. (B) The number of EEG spikes per day and the percent of time spent in seizures are plotted in this figure for rats with latent periods of at least 2 weeks. The data from each rat is shown in a different color. Closed circles illustrate seizure time (left y-axis) and open circles show the number of spikes per day (right y-axis). In six of seven rats, rapid increases in spikes preceded similar rises in seizure time. Reprinted with permission from reference 34.