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Research Paper

A decrease of ripples precedes seizure onset in mesial temporal lobe epilepsy☆

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ABSTRACT

High-frequency oscillations (HFOs) are promising biomarkers for epileptic foci; however, their characteristic changes during the preictal period remain unclear. Here, the preictal HFOs were recorded and detected by an automated HFOs detection method in the mouse pilocarpine model as well as in patients with mesial temporal lobe epilepsy (mTLE) and neocortical epilepsy. A total of sixteen low-voltage fast (LVF) and fifty-three hypersynchronous-onset (HYP) seizures were recorded in ten mice. The rate of ripples (80–250 Hz) decreased during 1 min before the onset of LVF and HYP seizures, which was primarily due to the reduction of type II (independent of epileptiform discharges) rather than type I ripples (superimposed on epileptiform activities). The ripple rate decreased until 30 s before HYP seizure, whereas it increased with a peak at 40 s during the 1 min preictal period of LVF seizures. Furthermore, the "ripple reduction" phenomenon was also observed in all twelve seizures from nine patients with mTLE but not in neocortical epilepsy. These results indicate that ripples may potentially be helpful for understanding the mechanisms of ictogenesis in mTLE, and the different modes of ripple changes during the minute before LVF and HYP seizures might also be beneficial for the diagnosis of seizure types.
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1. Introduction

Patients with mesial temporal lobe epilepsy (mTLE) have a high risk of developing pharmacoresistance. The unpredictable nature of seizure attacks will strongly impair patients' health and social functioning, imposing a major burden on their families. Finding specific ictal biomarkers is necessary and important for patients' safety. Furthermore, early and reliable ictal biomarkers may be necessary for the timely delivery of neuromodulation in a closed-loop manner. It has recently been reported that using optogenetics with closed-loop seizure detection for real-time, spatially-restricted therapeutic intervention can control spontaneous seizures in TLE only when it is delivered immediately following seizure onset (Krook-Magnuson et al., 2013). Also, we previously reported that the efficacy of low-frequency stimulation (LFS) for seizure control is more prominent in the initial few seconds (0–4 s) following seizure onset while delayed delivery of LFS is less effective or even aggravates seizures (Wang et al., 2008; Wu et al., 2008; Xu et al., 2010).

High-frequency oscillations (HFOs, 80–700 Hz) are a promising EEG biomarker of epilepsy. Accumulating evidence has shown that interictal HFOs, especially fast ripples (250–700 Hz), are closely associated with the seizure onset zone (Bragin et al., 2002; Jacobs et al., 2009a; Jirsch et al., 2006; Wang et al., 2012; Worrell et al., 2004) and the epileptogenic zone (Akiyama et al., 2011; Fujiwara et al., 2012; Jacobs et al., 2010). Recently, an increase of HFOs following seizure onset *in vivo* and *in vitro* has been reported (Khosravani et al., 2005; Levesque et al., 2012; Timofeev and Steriade, 2004), suggesting HFOs are also associated with ictogenesis. Therefore, analyzing the dynamic changes of preictal HFOs may not only help predict seizures, but also shed new light on the mechanisms of ictogenesis. So far preictal changes of HFOs have been described in a few reports, but contradictory conclusions are drawn from the results of Khosravani (an increase in high-frequency

Abbreviations: mTLE, mesial temporal lobe epilepsy; HFOs, high frequency oscillations; LVF, low-voltage fast; HYP, hypersynchronous; ANOVA, one-way analysis of variance; SE, status epilepticus; SOZ, seizure onset zone; IISs, interictal spikes; PP, primary propagation.

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band power at 8 s preictally) and Jacobs (preictal HFOs showing irregular trends) (Jacobs et al., 2009b; Khosravani et al., 2009). This contradiction may be due to the differences in epilepsy types enrolled in their studies. Moreover, Levesque et al. have recently reported that ripples predominate in low-voltage fast (LVF) onset seizures and fast ripples predominate in hypersynchronous-onset (HYP) seizures in animal models of TLE (Levesque et al., 2012), which suggests different subtypes of HFOs change in specific ways in different types of epilepsy. Thus, preictal changes in different types of HFOs need to be studied carefully in different forms of epilepsy. Here, we studied the dynamic changes of HFOs in preictal periods in a classical mouse pilocarpine model of mTLE (Curia et al., 2008) as well as in patients with mTLE who underwent invasive EEG recording. We also compared the findings with those in patients with neocortical epilepsy.

2. Materials and methods

2.1. Animals and surgery

Male ICR mice (30–35 g, Grade II, Experimental Animal Center, Zhejiang Academy of Medical Science, China) were intraperitoneally injected with scopolamine methylnitrate (1 mg/kg, Sigma) followed 30 min later by pilocarpine hydrochloride (200 mg/kg, i.p., Sigma). Status epilepticus (SE) was terminated after 1 h of continuous seizures by diazepam (1 mg/kg, i.p.). After 15 days of recovery, the surviving animals were anesthetized with pentobarbital (50 mg/kg) and mounted in a stereotaxic apparatus (SR-5N, Narishige, Japan). Bipolar electrodes made of stainless-steel Teflon-coated wires (791,500, A.M. Systems, USA; diameter 0.125 mm; distance between exposed tips, 0.5 mm) were implanted into the unilateral CA3 subfield of hippocampus (AP, −2.8; ML, −3.0; DV, −3.5) and entorhinal cortex (AP: −4.6, ML: −3.0, V: −3.7). The reference and ground screws were placed in the bone over the cerebellum. Then the recording and reference electrodes were welded to a receptacle, which connected the electrodes to recording wires for EEG recording. All experiments were carried out in accordance with the ethical guidelines of the Zhejiang University Animal Experimentation Committee and were in complete compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. EEG recording and data acquisition in mice

Mice surviving three week post-SE were housed individually in Plexiglas boxes (30 × 30 × 40 cm) under controlled conditions (12 h light/dark schedule). Food and water were provided *ad libitum*. Mice were habituated for 24 h before EEG recording by a PowerLab system (AD Instruments, USA) with sampling rate of 4 kHz and bandwidth of 0.5–1000 Hz. And a montage was used to diminish those artifacts recorded from two electrode tips. All mice were recorded 24 h/day for 10 days.

2.3. Intracranial EEG recording in patients

The patients' EEG data were collected in the Epilepsy Center, Second Affiliated Hospital, School of Medicine, Zhejiang University, and the Cleveland Clinic Epilepsy Center (study number 10–171). The patients with medically intractable epilepsy (Supplementary Table 1) underwent invasive EEG evaluation by either stereotactic EEG or a subdural grid and supplementary depth electrodes. The depth electrodes were composed of cylindrical platinum electrodes which had several contacts, ranging from 8 to 16. In addition, the contacts were 2.5 mm long, 0.8–1.1 mm in diameter, and 4–5 mm apart center-to-center. Each subdural contact had a diameter of 4 mm with a center-to-center separation of 10 mm. A three-dimensional reconstruction map was made to show the locations of the electrode contacts after implantation. Intracranial EEG was analyzed by at least two epileptologists. The areas showing the earliest intracranial EEG change in a seizure, such as the onset of repetitive spikes, background suppression, or paroxysmal fast activity, were defined as the seizure-onset zone (SOZ). Each selected patient had a confined SOZ for all recorded seizures either in mesial temporal structures or in neocortical area. All seizures were recorded routinely on reduced or no anti-epileptic medication at a sampling rate of 2000 Hz (bandwidth, 0.016–2000 Hz).

2.4. Distinction of electrographic seizure and seizure onset

Based on Bragin et al. (Bragin et al., 2005), an electrographic seizure was defined by a period of consistent, repetitive changes in the amplitude and frequency of electrical activity, and this activity was clearly distinct from inter-ictal activity. To exclude the interference from other neighboring seizures, only EEG seizures that were longer than 30 s and were seizure-free for at least 1 h before and after the seizure event were selected. Seizure onset was determined visually by the first sign of persistent changes distinct from the inter-ictal background. A consensus was made by two reviewers (C.L.X and Y·W).

2.5. Automated detection of HFOs with further visual confirmation

Type I ripple (superimposed on an inter-ictal spike or fast activity) and fast ripple were automatically detected according to Dümpelmann et al. (Dumpelmann et al., 2012). Briefly, EEG data with manually labeled type I ripple, type II ripple and fast ripple were imputed and filtered with a FIR equirriple filter at 80–700 Hz, and then the signals were divided into 10 ms-long subsets. Three features were derived and further labeled each subset. The features one and two reflect the increased signal amplitude during an HFO, in which the first feature was based on the increased signal energy of the signal during an HFO by estimating the short time energy; the second feature being sensitive for the increased signal amplitude was the short time line length. The third feature reflects the lower and more stable signal frequency of the signal during an HFO. Then subsets of features were selected as input vector for SVM for training, and the final model could detect all the manually labeled type I ripple and fast ripple, thus it could be used for automated type I ripple and fast ripple detection with high precision. Type II ripples (independent of epileptiform discharges) were more likely to be linked with normal EEG activities, and the majority of labeled type II ripples couldn't be detected by this SVM classifier. It suggested that SVM classifier was not suitable for type II ripple detection due to its low precision. Therefore, we used SVM classifier merely for type I and fast ripple detection. And a few type II ripples which were detected by SVM classifier were excluded.

For type II ripple only, we carried out another program based on the principles for visual detection of type II ripple (Wang et al., 2012). Firstly, EEG data were imputed with band pass filtered at 80–250 Hz. Secondly, signals containing at least five consecutive oscillations in the filtered band were separated and selected. Thirdly, selected signals were under further "denoising", *i.e.*, signals that had "false" oscillations such as non-sinusoidal harmonics caused by filtering sharp spikes and artifacts (Benar et al., 2010) were excluded, and fourth, selected signals which did not have three times higher in amplitude compared with background were excluded. All these above procedure were automatically carried out by computer program. Then, the left detected signals were extracted for further identification under manually time-frequency analysis, the time-frequency map of a true ripple event must show a primary isolated peak in the frequency range of 80–250 Hz. At last, type II ripples were selected based on their characteristics from these true ripples and labeled. All manually work was done by two experienced researchers and a consensus was made (C.L.X and S.W.). By using this method, we could detect all manually labeled type II ripple. Schematics of the automated detection method of type II ripple and representative type I, type II and fast ripple were shown in Fig. 1.

Interictal spikes without HFOs are thought to be closely related with epilepsy, and might be a different biomarker from HFOs (Levesque et al.,

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