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Review article

High-frequency oscillations and mesial temporal lobe epilepsy

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HIGHLIGHTS

- High-frequency oscillations reflect the activity of networks that sustain seizures and could serve as biomarkers of epilepsy.
- We review here the recent findings on the cellular mechanisms of ripples and fast ripples in mesial temporal lobe epilepsy.
- We also address the effects of anti-epileptic drugs in animal models and patients.
- We raise some questions and issues related to the definition of high-frequency oscillations.

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ABSTRACT

The interest of epileptologists has recently shifted from the macroscopic analysis of interictal spikes and seizures to the microscopic analysis of short events in the EEG that are not visible to the naked eye but are observed once the signal has been filtered in specific frequency bands. With the use of new technologies that allow multichannel recordings at high sampling rates and the development of computer algorithms that permit the automated analysis of extensive amounts of data, it is now possible to extract high-frequency oscillations (HFOs) between 80 and 500 Hz from the EEG; HFOs have been further categorised as ripples (80–200 Hz) and fast ripples (250–500 Hz). Within the context of epileptic disorders, HFOs should reflect the pathological activity of neural networks that sustain seizure generation, and could serve as biomarkers of epileptogenesis and ictogenesis. We review here the presumptive cellular mechanisms of ripples and fast ripples in mesial temporal lobe epilepsy. We also focus on recent findings regarding the occurrence of HFOs during epileptiform activity observed in *in vitro* models of epileptiform synchronization, in *in vivo* models of mesial temporal lobe epilepsy and in epileptic patients. Finally, we address the effects of anti-epileptic drugs on HFOs and raise some questions and issues related to the definition of HFOs.

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1. Introduction

Epilepsy is the most prevalent neurological disorder according to the World Health Organization, with a prevalence of over 50 million and an incidence of 2.4 million per year. Focal epileptic disorders represent 60% of these cases, with mesial temporal lobe epilepsy (MTLE) being the most prevailing syndrome. MTLE is characterised by seizures that recur following a latent period of up to many years after an initial brain insult such as *status epilepticus* (SE), traumatic brain injury, encephalitis or febrile convulsions [1,2]. These recurrent seizures originate from the hippocampus, entorhinal cortex (EC) or amygdala [3] and are often refractory to medication, making surgical resection of epileptic tissue the only therapeutic alternative [4]. Epileptologists are therefore trying to find biomarkers of MTLE that will lead to a better delineation of the seizure onset zone as well as to a better understanding of the disease. Approximately 15 years ago, the analysis of EEGs obtained from epileptic patients and from animal models mimicking this disease revealed the occurrence of high-frequency oscillations (HFOs) that appeared to be closely related to the paroxysmal activity generated from the epileptic tissue [5]. These HFOs have been categorised by many investigators into two groups, based on their frequency content: (i) ripples that comprise events between 80 and 200 Hz and (ii) fast ripples that include events between 250 and 500 Hz [6]. Ripples were initially discovered in the hippocampus of control animals during periods of immobility and consummatory behavior [7] but they are also observed in the epileptic tissue [6,8,9]. In addition, in both non-epileptic animals [10] and humans [11,12], fast ripples are recorded in the somatosensory cortex during sensory evoked potentials. In the epileptic tissue, fast ripples have been found in hippocampal and para-hippocampal regions [10,11,20,21], and in seizure onset zones [16,17].

Here, we will first address the cellular mechanisms that are presumably underlying ripples and fast ripples. Next, we will review data obtained from *in vitro* and *in vivo* experiments as well as from clinical studies in which the roles of HFOs in ictogenesis and epileptogenesis have been analysed. Then, we will consider the changes in HFOs that occur during treatments with anti-epileptic drugs (AEDs), and finally we will discuss some issues that are related to the definition of HFOs.

2. Ripples (80–200 Hz)

2.1. Cellular mechanisms

Under physiological conditions, ripples are mainly recorded from immobile or sleeping animal [16], and are often phase-locked to the negative phase of sharp waves in the pyramidal cell layer of the CA1 subfield of the hippocampus [7,19]. It has been proposed that ripples may be triggered by population bursts of highly interconnected CA3 neurons that would induce excitatory postsynaptic potentials (EPSPs) on pyramidal cells and on interneurons located in CA1 [20]; the depolarization of CA1 interneurons would then trigger high-frequency firing from basket cells and chandelier cells thus leading to the generation of inhibitory postsynaptic potentials (IPSPs) in CA1 pyramidal cells [28]. In line with this view, the spatiotemporal summation of IPSPs would result in a field potential oscillation at approximately 200 Hz [7,19], and thus ripples would mirror summated, Cl^--dependent IPSPs generated by pyramidal (principal) cells. GABAergic transmission is therefore thought to highly contribute to the generation of these oscillations [19,21,22].

However, other studies have indicated that ripples may be independent of GABAergic transmission and may instead rely on EPSPs generated in CA1 pyramidal neurons [23]. There is also evidence suggesting the involvement of gap junctions in ripple generation, since in *in vitro* preparations the application of gap junction blockers – such as octanol, halothane or carbenoxolone – reversibly suppresses ripple activity in the CA3 subfield [24]. Moreover, ripples recorded *in vivo* in the somatosensory cortex of anesthetized animals are suppressed within a few minutes after the administration of halothane and progressively reappear when its administration is stopped [25]. These results thus support *in silico* studies which have shown that the ripple generation depends on gap junctions between pyramidal cells, without the participation of chemical synapses [26]. It has also been proposed that gap junctions between interneurons synchronize subgroups of interneurons, thus promoting the synchronous firing of interneuronal populations and the increase of coherence of oscillations emerging from GABAergic neuronal networks [27]. However, this view is challenged by *in vitro* evidence showing that gap junction blockers do not block ripples recorded in the dentate area during pharmacological blockade of $GABA_A$ receptors [28]. Ripples can also be recorded in the *stratum pyramidale,* where parvalbumin-positive interneurons are not connected trough gap junctions [29] and patch-clamp experiments have demonstrated that the phase-locking relationship between interneurons and ripples is abolished after puffing gabazine on their somatic region [29]. Gabazine, a $GABA_A$ receptor antagonist, does not block gap junctions.

2.2. Epileptogenesis

Ripples have been linked to epileptogenesis due to their occurrence in structures that, under normal conditions, do not generate them. For instance, in non-epileptic animals, ripples are never observed in the dentate gyrus. However, in kainic acid-treated or in pilocarpine-treated epileptic animals, ripples can be recorded from this region [20,21] and their occurrence during the latent period (before the first spontaneous seizure) has been used to predict seizure occurrence. Accordingly, all animals presenting with pathological ripples in the dentate gyrus eventually generate spontaneous seizures, suggesting that ripples reflect abnormal network activity in this structure [15]. In addition, during the chronic period (*i.e.*, after the occurrence of the first spontaneous seizure), we have found in pilocarpine-treated epileptic animals that the occurrence of interictal spikes associated with ripples in the dentate gyrus can also be a marker of progressing epileptogenesis since their rates significantly increase over time [21]. It should be emphasized that ripples also occur in other structures of the temporal lobe – such as the CA3 subfield of the hippocampus, the EC and the subiculum – either in association with interictal spikes or independently of them [21] (Fig. 1A, C). When they occur in association with interictal spikes, their highest probability of onset is during the first phase of interictal spikes, before the peak [14,30] (Fig. 1B).

Several studies performed in epileptic patients have shown that when HFOs recorded from the seizure onset zone and from regions outside of it are compared, ripples are better biomarkers than interictal spikes to localize the former (*i.e.*, the brain area from which seizures initiate) [9,31,32]. However, ripples are not highly spe-

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