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Mechanisms of physiological and epileptic HFO generation

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ABSTRACT

High frequency oscillations (HFO) have a variety of characteristics: band-limited or broad-band, transient burst-like phenomenon or steady-state. HFOs may be encountered under physiological or under pathological conditions (pHFO). Here we review the underlying mechanisms of oscillations, at the level of cells and networks, investigated in a variety of experimental *in vitro* and *in vivo* models. Diverse mechanisms are described, from intrinsic membrane oscillations to network processes involving different types of synaptic interactions, gap junctions and ephaptic coupling. HFOs with similar frequency ranges can differ considerably in their physiological mechanisms. The fact that in most cases the combination of intrinsic neuronal membrane oscillations and synaptic circuits are necessary to sustain network oscillations is emphasized. Evidence for pathological HFOs, particularly fast ripples, in experimental models of epilepsy and in human epileptic patients is scrutinized. The underlying mechanisms of fast ripples are examined both in the light of animal observations, *in vivo* and *in vitro*, and in epileptic patients, with emphasis on single cell dynamics. Experimental observations and computational modeling have led to hypotheses for these mechanisms, several of which are considered here, namely the role of out-of-phase firing in neuronal clusters, the importance of strong excitatory AMPA-synaptic currents and recurrent inhibitory connectivity in combination with the fast time scales of IPSPs, ephaptic coupling and the contribution of interneuronal coupling through gap junctions. The statistical behaviour of fast ripple events can provide useful information on the underlying mechanism and can help to further improve classification of the diverse forms of HFOs.

Contents

Abbreviations: α, alpha (rhythm or oscillation); AMPA, 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl)propanoic acid, a subtype of ionotropic glutamate receptors; AP, action potential; β, beta (oscillation); CA, cellular automata; ECoG, electrocorticogram; EEG, electroencephalogram; GABA, gamma amino butyric acid; $GABA_A$, ionotropic gamma amino butyric acid receptor; γ, gamma (oscillation); HFO, High Frequency Oscillation; Hz, Hertz (cycles per second); I_h, the h-current, a depolarizing, cationic current activated by hyperpolarization; IPSC, inhibitory postsynaptic current; IPSP, inhibitory postsynaptic potential; KA, kainic acid; LFP, local field potential; MEG, magnetoencephalogram; mGluR, metabotropic glutamate receptor; μ, mu (oscillation); NMDA, *N*-methyl *D*-aspartate, a subtype of ionotropic glutamate receptor; pHFO, pathological high frequency oscillation; SPWR, sharp-wave ripples; TLE, temporal lobe epilepsy.

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1. Introduction

High frequency oscillations (HFOs) constitute a novel trend in neurophysiology that is fascinating neuroscientists in general, and epileptologists in particular. But what are HFOs? What is the frequency range of HFOs? Are there different types of HFOs, physiological and pathological? How are HFOs generated? Can HFOs represent temporal codes for cognitive processes? These questions are pressing, to which this review paper attempts to give constructive answers. In these introductory remarks we will consider the most basic question: what are HFOs and how should these be designated? To deal with this question it is useful to consider briefly how neurophysiologists have characterized neuronal oscillations in general, as reflected in local field potentials and therefore in EEG and MEG signals.

Since the early days of human neurophysiology scientists have been fascinated by the variety of oscillations that may be recorded from the scalp and directly from within the brain. Empirically a classification of these oscillations in a series of frequency bands emerged, which were designated by Greek letters ($\delta, \theta, \alpha/\mu, \beta, \gamma$) a classification that was supported by multivariate statistical analysis of EEG spectral values in the seventies (Lopes da Silva, 2011). Nonetheless the limits of the EEG frequency bands are fuzzy. Ultra-slow (near-DC) oscillations (Aladjalova, 1957; Vanhatalo et al., 2004) and ultra-fast frequency components have also been described. Here we concentrate primarily on the fast frequency components.

In the early descriptions of EEG the issue of frequency components higher than about 30 Hz was an unchartered continent. Two main factors changed this picture in the last three decades: (i) the rise of broad-band digital EEG, which made possible recording of signals beyond the traditional low-pass filtered EEG at 70 Hz, extended the recordings to frequencies as high as 500 Hz and beyond; (ii) novel findings in animal neurophysiology showing the existence of oscillations at frequencies in the γ band range of 38–100 Hz in several cortical and subcortical brain areas (for early literature on this subject see Bressler and Freeman (1980)). Currently, while there is some disagreement on whether the term HFO includes the γ frequency range, perhaps the most general usage is γ for frequency components between 30 and 100 Hz, and HFOs for frequencies beyond 100 Hz. However, we will review some aspects of γ oscillations, partly because they shed some light on HFO mechanisms, and partly because there can be overlap between γ and "ripples", a transient hippocampal HFO in the 100 Hz to 200–250 Hz band. Functionally γ and ripples can coexist under physiological conditions and share mechanisms (Sullivan et al., 2011), or can be linked under the term fast γ (90–150 Hz, with slow γ at 30–50 Hz and mid γ 50–90 Hz) (Belluscio et al., 2012), while other authors call oscillations from ~60 to 200–250 Hz "high γ" (Crone et al., 2006; Edwards et al., 2005).

Among physiological HFOs a number of specific phenomena attracted particular attention: γ oscillations around 40 Hz in the visual cortex associated with visual perception (reviewed in Singer and Gray (1995)), and in the sensorimotor cortex related to motor activity (Murthy and Fetz, 1996). The former were proposed to form the mechanism by which various features of a visual scene may be bound together into a percept—the "binding hypothesis". Beyond this observation, it was also shown that γ oscillations may operate as a general mechanism that is capable of binding together, by a process of phase synchronization, not only the firing of neurons at the local level, but also neural activities of spatially separate cortical areas (Roelfsema et al., 1997). Furthermore, the discovery of hippocampal ripples during behavioral immobility, consummatory behaviors and slow-wave sleep (Buzsáki et al., 1992), kindled the interest for understanding the functional significance of HFOs in the process of memory consolidation. The subsequent finding that similar short transient oscillations, named "fast ripples", can be observed in the local field potential recorded from the hippocampus and the temporal cortex of epileptic humans and rodents (Bragin et al., 1999b) stimulated the interest for these oscillatory phenomena as possible biomarkers of epileptogenic neural networks. These high frequency components recorded in local field potentials (LFPs), electrocorticograms (ECoG) and EEG/MEG signals received, collectively, the designation of HFOs.

We should note, however, that these terms are purely descriptive and do not have a precise definition. The term HFO can mean phenomena with a variety of characteristics: HFOs may be band-limited or broad-band, transient (burst-like) phenomenon or steady-state, event-related or not. Furthermore, HFOs may be encountered under physiological or under pathological conditions; for the latter the symbol pHFO has been used. This, however, is a secondary characterization that depends on the demonstration that this kind of HFO is significantly associated with a pathological brain condition such as epileptogenicity. One proposal distinguishes these pHFOs from physiological kinds of HFOs according to frequency content ("fast ripples" *vs* "ripples") (Bragin et al., 1999b), and is currently a matter of intense experimental scrutiny.