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REVIEW

Electrographic high-frequency activity and epilepsy

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Summary High-frequency electrographic activity (HFA) has a frequency of 80—600 Hz. It can be observed interictally in epileptic foci and also at the onset of epileptic seizures. There are several hypotheses about how HFA is generated, and it has been suggested that the underlying mechanisms may play an important role in epileptogenesis and ictogenesis. The high specificity of HFA for epileptic foci is now used during presurgical evaluation to help localize epileptic focus. In this article we review the current state of knowledge regarding this phenomenon and challenges for the future studies focusing on HFA.

Contents

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Introduction

High-frequency cortical activity (>80 Hz) was a major discovery made in last fifteen years in epilepsy research. The suggestion that population neuronal activity at high frequencies may be involved in epileptogensis and seizure genesis led to increased interest in this phenomenon in experimental and clinical epileptology. High frequency activity (HFA) has provided much new information, but has also introduced many controversies and unanswered questions. Some of the recent advances in HFA research and remaining challenges for the future are discussed.

Classification and terminology

In vitro and in vivo studies and recordings in humans revealed the presence of several different types of high-frequency activities in brain (Allen et al., 1992; Bikson et al., 2003; Bragin et al., 1999a,b; Buzsaki et al., 1992; Csicsvari et al., 1999a; Draguhn et al., 1998; Dzhala and Staley, 2004; Fisher et al., 1992; Khosravani et al., 2005; Ylinen et al., 1995). Often they are called fast activities or high-frequency oscillations. There were further attempts to subclassify high-frequency activities in different frequency bands. One subgroup of HFA is the ripple, which was originally described as physiological activity in hippocampus (Buzsaki et al., 1992); its frequency is in the band 80—200 Hz. A second subgroup is the fast ripple, which was observed in epileptic tissue and has frequency 250—500 Hz (Bragin et al., 1999b, 2004). However, the distinction between the two is not as clear as these figures suggest: pathological HFA found in epileptic tissue can have slower frequencies than 200 Hz (Worrell et al., 2004), and physiological HFA can exceed 600 Hz (Baker et al., 2003). Therefore, research continues to improve the classification and interpretation of HFA. The classification of HFA has largely relied on power spectral analysis; the use of other criteria may improve the characterization and definition of HFA subtypes, and lead to better insight into the mechanisms of HFA. However the problem may be complicated if physiological and epileptic HFA of similar frequencies were to share common mechanisms.

Mechanisms of high-frequency activity

There are several theories, supported by experimental data, on the possible mechanisms of HFA. First, the interneuron theory suggests that high frequency oscillations from ripple band result from summation of IPSPs on pyramidal cell neurons (Ylinen et al., 1995). In the hippocampal CA1 area, the activity of pyramidal neurons is partly controlled by the activity of interneurons via perisomatic inhibition. When interneurons fire action potentials at high-frequency, they produce IPSPs in the postsynaptic pyramidal cells. These fast IPSPs then create a time window during which pyramidal cell are able to fire action potentials (Fig. 1A). The activity of one interneuron can influence the action potential firing of several pyramidal cells which can therefore cause synchronous firing of these cells (Csicsvari et al., 1999b). The resulting summation of IPSPs on the pyramidal cells generates a low-amplitude high-frequency extracellular field potential which is manifested as a high-frequency oscillation.

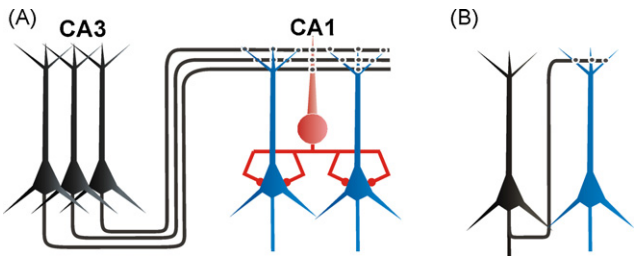

Figure 1 Synaptic mechanisms of HFA. (A) Mechanisms of sharp-wave ripples. Pyramidal cells from CA3 (black) project on to interneurons (red) and pyramidal (blue) cells in CA1 and create EPSP which generates a sharp wave. Fast spiking interneurons projecting to pyramidal cell generate fast IPSPs onto pyramidal cells, controlling their action potential firing which results in ripple component of sharp-wave complex. (B) Two interconnected pyramidal cells. Activity in one cell (black) projects to the adjacent cell (blue) resulting in depolarization. This then may lead to synchronous action potential firing. In epilepsy this mechanism may be further promoted because of sprouting of axon collaterals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

This process runs in parallel with excitatory input from CA3 which activates both pyramidal cells and interneurons. The phenomenon which results from these processes is called sharp wave ripples. It was suggested that this mechanism is predominantly involved in memory formation and cognitive processing and enables coupling between pyramidal cells, which may underlie memory formation and re-activation processes (Csicsvari et al., 2007).

The second theory suggests that high-frequency oscillations are due to synchronous action potential firing of a group of principal cells (pyramidal cell or granule cells). Each individual high-frequency cycle represents a population spike, but none of the principal cells fires on every cycle. Each population spike probably is generated by small group of principal neurons. The underlying mechanisms responsible for the synchronous firing of pyramidal cells is unclear; but the synchronizing mechanisms must be sufficiently fast to enable action potential co-firing during 2—5 ms window. Several candidate synaptic mechanisms are shown in Fig. 1.

One candidate mechanism is excitatory coupling between pyramidal cells. Activation of one pyramidal neuron would result in an EPSP and subsequent depolarization at postsynaptic pyramidal neurons, which produces synchronous firing of synaptically coupled neurons (Dzhala and Staley, 2004). In the epileptic hippocampus underlying morphological changes may exacerbate this mechanism. One such change is the sprouting of axons and axon collaterals which results in the formation of new synaptic connections between adjacent neurons and even autapses; on the network level this results in the formation pathologically interconnected neuronal clusters (Bragin et al., 2000). This results in an increase in the effectiveness of fast excitatory synaptic coupling (Fig. 1B).

Another mechanism that enables fast synchronous neuronal firing is electrotonic coupling (Dudek et al., 1986). An action potential in one pyramidal cell may propagate