Clinical Neurophysiology 117 (2006) 2111–2117

www.elsevier.com/locate/clinph

Invited review

Fast activity as a surrogate marker of epileptic network function?

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Accepted 24 February 2006
Available online 14 July 2006

Abstract

The detection of epileptiform discharges in electroencephalography recordings is a crucial part in diagnosing epilepsy. Thorough electrophysiologic evaluation yields information that allows for tailored surgical therapy in many cases, and thus improves treatment outcome. In recent years, fast activity (>60–80 Hz) has been investigated for its diagnostic value in addition to well-known patterns such as epileptic transients. It was shown that these high frequency oscillations are highly specific for epileptic network function and might provide valuable information for localization of epileptic networks and understanding of their mechanisms. In this review, an overview of the electrophysiologic characteristics, putative cellular and network mechanisms in epilepsy is given. Recent studies are reviewed and interpreted in the context of a common hypothetical model.

Keywords: Epilepsy; Electroencephalography; Magnetoencephalography; High-frequency oscillation; Fast activity

1. Introduction

One of the most important aspects of brain research is the detection and interpretation of dynamics of normal and abnormal functions. The investigation of these dynamic systems requires analyses with high spatio-temporal resolution. Because electrophysiology may contribute markedly, feasibility of new methods and new electrophysiologic targets may open new windows to dynamics of brain function. Recent findings suggest that among these, fast cortical oscillations as pathophysiological targets seem especially interesting for the investigation of epilepsy.

Electric signals from the brain represent the superposition of various neural systems, both physiological and pathophysiological, constituting a dynamic system, additionally influenced by external and internal factors such as sensory input, circadian rhythms, pharmacological therapy and individual susceptibility. The difficulty a diagnostic electrophysiologic modality, such as electro (EEG)- and magnetoencephalography (MEG), has to master is the extraction of the subset of abnormal components in this mixed system. An additional problem is the signal strength of these components. For any activity to be directly visible in surface EEG or MEG, synchronization of a large neural network is necessary. For example, an epileptic transient is only visible, when at least 6–10 cm^2 of cortex or even larger neuron populations are synchronously activated (Tao et al., 2005).

The underlying mechanisms of epileptic synchronization can be summarized by the concept of a more or less complex synchronizing signal that originates from the epileptogenic network and spreads throughout connected subnetworks. The spread of activation requires a certain amount of time before enough neurons are affected to produce transients on the surface. It is therefore likely, that the signal is present before transients or even without them, when the spreading activation does not reach enough neurons or the increased activity is not accompanied by sufficient synchrony. The corresponding waveform would then be contained in background activity, superimposed by physiological and environmental noise, effectively resulting in ''epileptic silence'' on the surface. In addition

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1388-2457/$32.00
doi:10.1016/j.clinph.2006.02.023

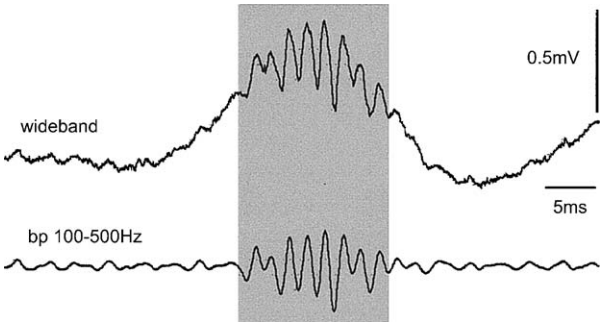

Fig. 1. Spontaneous high-frequency oscillation (HFO) events from continuous wideband EEG recordings, wideband data and 100–500 Hz bandpass filtered data is shown (from Bragin et al., 2002a,b used with permission).

to that, too little recording bandwidth and too gross electrodes might also result in decreased detectability.

What activity could be suitable to take the role of such a synchronizing signal? Recent research in normal brain function might provide an answer. To integrate components of internal information and sensory input into the context of general brain state, oscillations in various frequency ranges provide an effective mean and seem to be able to synchronize large neuronal ensembles (Curio et al., 1994; Jones and Barth, 1999; Jones et al., 2000; Engel and Singer, 2001; Kahana et al., 2001). Pathological activity is seen similar to and overlapping with physiological oscillations. These electromagnetic oscillations in frequency bands above traditional ranges (high frequency oscillations, "HFO") used in EEG investigations were seen during both putative silent intervals and intervals with epileptiform waves (Traub, 2003). Such "ripples", as the activity was termed, originate from brain areas close to the epileptogenic network (Bragin et al., 1999b, 2002a,b; Traub et al., 2001; Grenier et al., 2001) and might prove to be a novel surrogate marker of epileptic network function (Fig. 1).

2. Investigated areas and species

In normal brain, HFO in a frequency range of 80–200 Hz (ripples, "R") have been described in the cornu ammonis region (CA) of the hippocampus (Hip), in parahippocampal regions and the entorhinal cortex (EC) of rats (Buzsaki et al., 1992; Ylinen et al., 1995; Csicsvari et al., 1999). Physiologic HFO in a frequency range around 600 Hz were also seen in human thalamic and cortical areas of the somatosensory system (Curio et al., 1994; reviewed in Curio, 2000).

Main brain areas investigated for high-frequency activity in an epileptic context have been hippocampus and entorhinal cortex of non-primates (Buzsaki et al., 1992) and of patients with temporal lobe epilepsy (Bragin et al., 1999a). Epileptic high-frequency oscillations were also recorded in neocortical areas of rodents (Kandel and Buzsaki, 1997), cats (Grenier et al., 2001) and in a slightly lower frequency range of 60–100 Hz in humans (Worrell et al., 2004). Differences due to epilepsy in evoked HFO (Curio et al., 1994; review in Curio, 2000) were also investigated in human somatosensory system (Kubota et al., 2004). In addition to the R range, HFO between 250 and 500 Hz (fast ripples, "FR") were found in epileptic rats, kindled and/or made epileptic through excitotoxic lesions (Bragin et al., 1999b).

To investigate qualitative characteristics and spatial structure of HFO generating networks, Bragin et al. (2002a,b) conducted a study using data from chronically implanted mircroelectrodes in EC of patients with mesial temporal lobe epilepsy (mTLE). The study demonstrated that R oscillations have different voltage versus depth profiles compared to FR: FR expose a polarity reversal in the middle layers of EC, while R only rarely show such a reversal in any EC layer. Bragin also describes that FR generating areas have a volume of about 1 mm^3 and that multiunit synchronization is significantly increased during FR oscillations compared to R. Based on these findings, it can be hypothesized, that the networks generating FR are more localized than those underlying R oscillations and are probably situated in the middle layers of EC. This is congruent with findings in the normal brain, which suggest that oscillations in higher frequency ranges originate from smaller networks compared to slow oscillations which are generated by rather large neuronal populations (Steriade, 2001; Csicsvari et al., 2003).

3. Electrophysiologic characteristics

In contrast to traditional EEG frequency bands which range up to 30 or 40–70 Hz when gamma band is included, high-frequency activity is defined as having a frequency of more than 60–80 Hz. The upper bound of the high-frequency band is commonly set at about 500 Hz (Bragin et al., 1999a). Findings of several studies (Chrobak and Buzsaki, 1996; Bragin et al., 1999a; Grenier et al., 2001) also suggest the existence of a slower subband with bounds at around 80–160 Hz in human and 100–200 Hz in non-primate brain areas, possibly extending down to about 60 Hz in patients with neocortical epilepsies (Worrell et al., 2004). A faster subband is described with frequency limits at about 250–500 Hz (Bragin et al., 1999a,b). Background activity during HFO events can have a low amplitude (Draguhn et al., 1998) or show a physiological or epileptic transient excitatory pattern, on which HFO activity is superimposed (Bragin et al., 2002a,b; Staba et al., 2002).

Staba et al. investigated the high-frequency range in detail and were able to statistically differentiate the two subgroups (Staba et al., 2002). In this study, data from episodes of NREM sleep of patients with intractable temporal lobe epilepsy (TLE) were examined. Recordings were performed using intracerebral depth electrodes positioned in Hip and EC. The analysis included band-pass filtering with cutoff frequencies of 80 and 500 Hz and spectral analysis of data epochs with significant activity. It could be shown,