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Cellular mechanisms of high frequency oscillations in epilepsy: On the diverse sources of pathological activities

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Summary A major goal in epilepsy research is to understand the cellular basis of pathological forms of network oscillations, particularly those classified as high-frequency activity. What are the underlying mechanisms, and how do they arise? The topic of this review is the pattern of high-frequency oscillations that have been recorded in epileptic tissue, and how they might differ from physiological activity. We discuss recent experimental and clinical data with a major focus on the diverse sources of extracellular signals and the contribution of different neuronal populations, including GABAergic interneurons and glutamatergic principal cells.

Introduction

We have come a long way in our efforts to understand electroencephalographic (EEG) recordings from the initial studies of Berger (1929), to more recent studies analysing multielectrode recordings from deep in the brain, and sampling at up to 30 kHz. The computational demands for such recordings are of course large. But from these datasets we can derive a greater range of parameters, extending to higher frequency analyses and identifying spatial patterns, thereby enabling us to distinguish between different neurophysiological events from the local field potentials to large scale neuronal volumes at a large spectrum of frequencies (Buzsaki, 2006).

The relationship of various brain oscillations to particular brain states is well recognized. The method of recording is also important. Anaesthesia is associated with slow waves, similar to those recorded during slow-wave sleep (<2 Hz, Steriade, 2003); alpha rhythms (8—10 Hz) occur during relaxed wakefulness (Adrian and Yamagiwa, 1935) and theta activity (4—12 Hz) is predominant during low level mental activity and in exploratory behaviour and REM sleep (Soltesz and Deschênes, 1993; Bragin et al., 1995; Buzsáki, 2002). Most of these brain oscillations can be detected at the scalp, and are the major sources of surface EEG fluctuations. In contrast, other types of faster neuronal activity are more easily recorded as local field potentials, and exhibit particular spatial distributions in different brain structures. Gamma rhythms (30—80 Hz) in neocortex and the hippocampus are

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predominant during exploratory behaviour and perceptual tasks (Soltesz and Deschênes, 1993; Bragin et al., 1995; Csicsvari et al., 1999; Gray et al., 1989), whereas hippocampal ripples (80—200 Hz) appear to be instrumental in memory consolidation (Ylinen et al., 1995; Csicsvari et al., 2000; Dupret et al., 2010). Understanding the origin of these rhythms and their functional significance remains a major research goal.

A key objective in epileptology is to characterize the pathological forms of network oscillations. High-frequency activity, as noticed in epilepsy research, encompasses a large spectrum of oscillations. It extends from *brief* high-frequency oscillations termed fast ripples (250—800 Hz), which are recorded locally from the epileptogenic regions of the hippocampus and the temporal cortex of epileptic humans and rodents (Bragin et al., 1999b; Urrestarazu et al., 2007; Worrell et al., 2008), to *longer* epochs of slower activities (80—250 Hz) recorded at larger neuronal territories (Allen et al., 1992; Worrell et al., 2004; Jacobs et al., 2009). All these forms of activities have particular clinical significance due to their association with the onset of seizures and with interictal events in seizure prone individuals (Bragin et al., 1999a,b; Jacobs et al., 2009; Worrell et al., 2004; Khosravani et al., 2005; Schevon et al., 2009; Jiruska et al., 2010). Here we review recent data obtained by combining single-cell and multisite recording approaches aimed to uncover the cellular and network mechanisms responsible for diverse forms of high-frequency oscillations in epilepsy. We will mainly focus on the diverse sources of extracellular signals and the contribution of different neuronal actors to these rhythmopathies.

Cellular sources of extracellular activity

One important step in understanding the basic mechanisms of brain oscillations is to know how they are created at the extracellular field potential. EEG signals recorded at the scalp are thought to represent an average of predominantly synaptic activity over millimetres of cortex (Nunez and Srinivasan, 2006). The local field potentials, which constitute one major component of the extracellular EEG signals, result from transmembrane currents produced by several individual neurons (Nicholson and Freeman, 1975). Ohm's law tells us that these currents are proportional to the product of the conductance of the channels involved and their driving force (the reversal potential minus the membrane potential, $E_{rev} - E_m$). Hence, the contribution of the different generators to the ongoing EEG varies substantially depending on the type of activity, the brain state and the circuits involved. Also, while most of these signals may be present in intracranial EEG recordings using either macro- (up to 10 mm^2) or microelectrodes (up to 400 μm^2), action potential firing and decorrelated spontaneous synaptic activity from a large population of cells can only be probed with microelectrodes. Thus our ability to detect different activity patterns depends critically on the tools being used.

Stimulation of axonal tracts can elicit an easily recordable field event in the target structure (Lorente de No, 1947; Lomo, 1971). Timing considerations, including the latency and kinetics of this event, indicate that the local field potential corresponds to the postsynaptic compound glutamatergic current. This compound excitatory postsynaptic current (EPSC) is peculiarly visible in the local field potential presumably because many channels in a small volume of tissue are opened almost synchronously after artificial stimulation. The EPSC dynamic of the order of tens of milliseconds is slow enough to facilitate summation of the individual contribution from many parallel-oriented cells. Instead, action potentials are only visible as population spikes if they occur in many cells synchronously with millisecond precision, as might occur following high stimulation strengths (Andersen et al., 1971). Consequently, clinical data on evoked brain activity is thought to represent mainly postsynaptic glutamatergic currents and only rarely population spikes, with the exception of pathological situations of enhanced neuronal firing synchronization such as in epilepsy (Rutecki et al., 1989; Wilson et al., 1990; Valentín et al., 2002).

Until recently, the case for GABAergic currents contributing significantly to evoked field events has been less considered — although note the slow ''I-wave'' induced in the olfactory bulb following stimulation of the olfactory tract (Pickles and Simmonds, 1978), and classical work in the rodent hippocampus (Andersen et al., 1964). The last couple of years, however, has seen the publication of a number of studies showing clearly that spontaneous GABAergic currents are indeed visible in local field recordings using microelectrodes (Glickfeld et al., 2009; Trevelyan, 2009; Bazelot et al., 2010; Oren et al., 2010), and in some circumstances may even be the dominant current during ongoing activity (Trevelyan, 2009; Oren et al., 2010). A notable feature of the spontaneous inhibitory field potentials is that they may arise from the firing of single GABAergic interneurons, or very small populations of interneurons. In contrast, EPSCs elicited by action potentials of single pyramidal cells appear rather less visible in the field potential (Bazelot et al., 2010; Oren et al., 2010), although may be apparent from averaging many repeated events (Nauhaus et al., 2009).

The relative field visibility of synaptic potentials elicited by individual pyramidal cells and interneurons may be understood by considering the differences in their respective synaptic contacts. Extracellular EPSCs elicited by a single pyramidal cell are less visible possibly because glutamate is released over a distributed area, at low probability ($P_{release}$ typically about 0.4 at 2 mM Ca^{2+} and 1 mM Mg^{2+}, Hardingham et al., 2006) and quite low density. It is also relevant that the postsynaptic structures, the dendritic spines, are very small. When glutamate receptors (GluRs) open, the membrane potential collapses quickly on these small structures with only very small conductances being generated thereby reducing the effective driving force ($E_{glut} - E_m$) and the subsequent current flow (Jack et al., 1975). The currents consequently are far smaller than if the GluRs were located directly on large dendritic branches. Hence, field potential events resulting from firing from individual glutamatergic cells are less likely to be detected than inhibitory potentials, although spontaneous large events reflecting enhanced synaptic synchrony are recorded by the scalp EEG under certain phases of sleep (Amzica and Steriade, 1998; Cash et al., 2009). Under epileptic conditions, however, unbalanced inhibition and excitation significantly alter the nature of the extracellular signals and pathological synaptic events dominate the ongoing EEG. This is the case of interictal spikes of the order of several hundreds of millivolts, which