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Action potentials contribute to epileptic high-frequency oscillations recorded with electrodes remote from neurons

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HIGHLIGHTS

- Action potentials generating high-frequency oscillations (HFOs) are thought to be recordable only in the immediate vicinity of neurons.
- We showed that HFOs recorded with electrodes remote from neurons may be generated by clusters of action potentials.
- The phenomenon of action potentials that are recorded with electrodes far from neurons can possibly extend the clinical meaning of EEG.

ABSTRACT

Objective: The importance of epileptic high-frequency oscillations (HFOs) in electroencephalogram (EEG) is growing. Action potentials generating some HFOs are observed in the vicinity of neurons in experimental animals. However electrodes that are remote from neurons, as in case of clinical situations, should not record action potentials. We propose to resolve this question by a realistic simulation of epileptic neuronal network.
Methods: The rat dentate gyrus with sclerosis was simulated *in silico*. We computed the current dipole moment generated by each granule cell and the field potentials in a measurement area far from neurons.
Results: The dentate gyrus was stimulated through synaptic input to evoke discharges resembling interictal epileptiform discharges, which had superimposed HFOs $\leqslant$ 295 Hz that were recordable with remote electrodes and represented bursts of action potentials of granule cells. The increase in power of HFOs was associated with the progression of sclerosis, the reduction of GABAergic inhibition, and the increase in cell connectivity. Spectral frequency of HFOs had similar tendencies.
Conclusions: HFOs recorded with electrodes remote from neurons could actually be generated by clusters of action potentials.
Significance: The phenomenon of action potentials recorded with remote electrodes can possibly extend the clinical meaning of EEG.

1. Introduction

The importance of high-frequency oscillations (HFOs), particularly fast ripples >200 Hz, in the depth electroencephalogram (EEG) is growing ever since the discovery of HFOs recorded with depth electrodes (Jirsch et al., 2006). Evidence is now accumulating to indicate that pathologic HFOs in EEG have a closer relationship with epileptogenicity and/or ictogenicity than interictal epileptiform discharges (IEDs) or "epileptic spikes" have (Engel et al., 2009; Jacobs et al., 2010). However we still do not know the generative mechanisms of HFOs and the exact meaning of HFOs.

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Experimental pathologic HFOs recorded with microelectrodes are thought to be generated by action potentials of synchronously bursting principal cells and therefore represent recurrent "population spikes" (Bragin et al., 1999, 2011; Dzhala and Staley, 2004; Ibarz et al., 2010). Depth electrodes, however, are generally remote from neurons. This suggestion raises the question of whether action potentials can be really recorded with electrodes far from neurons, and this is even more questionable with reports that fast ripples are generated through the loss of correlation of cell activity (Foffani et al., 2007; Demont-Guignard et al., 2012), which indicates that amplitude of summated activity should be very low. Depth EEG is believed to represent the field potentials generated from neuronal membrane potentials, particularly postsynaptic potentials (PSPs) at dendrites, and not action potentials (Menendez de la Prida and Trevelyan, 2011). It is believed that fields generated by action potentials are visible only at approximately 10 μm from the generator, a distance much smaller than that between a depth electrode and any significant neuronal assembly (Bédard et al., 2006). The correspondence between action potentials and HFOs in local field potentials (LFP) has been studied only with microelectrodes (Bragin et al., 1999, 2011; Dzhala and Staley, 2004; Foffani et al., 2007; Ibarz et al., 2010). The reports of lack of relationship between electrode-size and HFO detection were regarding depth electrodes (Châtillon et al., 2011, 2013), and such relationship is still open with respect to microelectrodes. We hypothesize that at least part of the action potentials related to the generation of HFOs may contribute to remote potentials, which is so far unproved to our knowledge.

The behavior of individual neurons has been investigated by intracellular and extracellular recording. However, the relationship between neuronal membrane potentials and depth EEG findings is not easy to comprehend, as EEG recorded with electrodes remote from neurons represents summated field potentials with a considerably large spatial extent including innumerable neurons. Even when some part of an electrode is close to cells, the larger part of electrode is far away from those cells due to the size of the electrode. As computer simulation of neuronal network can be useful and possibly the only way to understand the correspondence between depth EEG discharges and behaviors of the whole neuronal network, we tried to address the above questions, particularly what clinical HFOs represent, through a realistic simulation of neuronal network. Although there are several simulation studies on LFP recorded with microelectrodes placed in the vicinity of neurons (Gold et al., 2006; Ibarz et al., 2010; Schomburg et al., 2012; Wendling et al., 2012; Buzsáki et al., 2012; Reimann et al., 2013), the simulation of fields seen through electrodes far from neurons has not yet been attempted.

The rat dentate gyrus is appropriate for this purpose. Pathological HFOs were observed with microelectrodes in association with sclerosis (Bragin et al., 2000). The effects of recurrent excitatory collateral synaptic connections on HFOs can be studied because synaptic connections between granule cells (GCs) do not exist in the healthy condition but are formed through mossy-fiber (GC axon) sprouting with sclerosis. As Bragin et al. (2002) performed electrical stimulations to evoke HFOs in the dentate gyrus in slice preparations, we simulated such experiments. In the present study, we could not model the actual physical properties of a macroelectrode, and therefore potentials were simply simulated as averaged fields in a measurement area that was far from neurons.

2. Methods

In a real rat dentate gyrus that spans 6 mm in the septotemporal axis, there are more than one million neurons, and the dentate gyrus is divided into lamellae of 600 μm each. The simulation of the rat dentate gyrus represented a three-dimensional structure of layers of neurons including 10,000 GCs and corresponding 300 mossy cells (MCs), 100 basket cells (BCs) and 120 hilar interneurons (HCs; hilar perforant-path associated cells, HIPP cells) with a spatial extent of 1 mm in the septotemporal and transverse axes. Somas of GCs were arranged to form the 60 μm-thick granule layer, and GCs projected dendrites into the molecular layer where they received the fibers from the perforant path. MCs were scattered in the polymorphic layer and BCs were along the border between the granule and polymorphic layers (Supplementary Fig. S1A). In this simulation, GCs and MCs were excitatory with mediation by the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor, and BCs and HCs were inhibitory through the fast γ-aminobutyric acid $(GABA)_A$ receptor. The simulation program was a modified version of that used by Morgan and Soltesz (2008) with web data base based on a program of Dyhrfjeld-Johnson et al. (2007), and therefore gap junctions could not be included in the simulation. The relative number of cells and axonal distribution were in conformity to Morgan and Soltesz.

The single cells were conductance-based multi-compartmental models containing multiple ionic currents, including sodium, fast- and slow-delayed rectifier potassium, A-type potassium, I_h, L, N, and T-type calcium, and calcium-dependent potassium, with confirmation of firing patterns corresponding to recording from electrophysiological experiments (Santhakumar et al., 2005). The number of compartments in a model cell was 9, 17, 17, and 13, respectively regarding GC, MC, BC, and HC, and the number of dendrites in a cell was 2, 4, 4, and 4, respectively. Parameters of cells within each subgroup of GC, MC, BC, and HC are common and not randomized. Mossy fiber sprouting was modeled by adding synaptic connections from GCs to the proximal dendrites of GCs. As in their simulation study, the probability of GC connection was modified for a preferential attachment, in which, at first, a half of the scheduled number of connections was randomly defined, and then the remaining connections were added so that the more connections a given cell already had, the more likely it would be to receive another connection (Barabási and Albert, 1999). The conduction delay including both the synaptic delay and the axonal conduction delay between GCs was at least 0.8 ms, and the added distance-dependent delay was 0.24-ms per 60-μm separation. The degree of cell connectivity in the current simulations was in conformity to previous reports (Buckmaster et al., 2002; Dyhrfjeld-Johnson et al., 2007; Morgan and Soltesz, 2008).

In a 10% stimulation paradigm, the perforant path synaptic input to the dentate gyrus was delivered to 1000 (10%) GCs and the corresponding numbers of other cells in a 600 μm-wide lamina (Morgan and Soltesz, 2008). The stimulations started 10 ms from the beginning of the session with temporal jitter within 2 ms. We computed the current dipole moment (Demont-Guignard et al., 2009) generated by each GC and the field potentials recorded with microelectrodes (each 25 μm-by-25 μm, an area of 625 μm^2) that were 1000 μm away from the border plane of molecular and granule layers in the direction of the molecular layer. The field generated by the other types of neurons was not computed because it is a closed field. Field potentials generated by every GC were summated over the electrodes under the quasi-static approximation. We assumed that the simulated field potentials corresponds to the signal induced by the network at the center of each microelectrode, that each GC functions as a point source (i.e., a current dipole formed by a sink and a source), and that all current dipoles are positioned within a volume conductor characterized by homogeneous conductivity (Supplementary Fig. S1B).

The potential V_i of the electric dipole associated with a cell i is

$$V_i = \frac{\vec{d}_i \cdot \vec{u}_i}{4\pi\sigma r_i^2}$$