

HIGH-FREQUENCY OSCILLATIONS AND NEOCORTICAL SEIZURES: DO THEY HAVE A ROLE IN SEIZURE ONSET, AND WHICH MECHANISMS GENERATE THEM?

Neocortical Very Fast Oscillations (Ripples, 80–200 Hz) During Seizures: Intracellular Correlates

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Multisite field potential and intracellular recordings from various neocortical areas were used to study very fast oscillations or ripples (80–200 Hz) during electrographic seizures in cats under ketamine-xylazine anesthesia. The animals displayed spontaneously occurring and electrically induced seizures comprising spike-wave complexes (2–3 Hz) and fast runs (10–20 Hz). Neocortical ripples had much higher amplitudes during seizures than during the slow oscillation preceding the onset of seizures. A series of experimental data from the present study supports the hypothesis that ripples are implicated in seizure initiation. Ripples were particularly strong at the onset of seizures, and halothane, which antagonizes the occurrence of ripples, also blocked seizures. The firing of electrophysiologically defined cellular types was phase-locked with ripples in simultaneously recorded field potentials. This indicates that ripples during paroxysmal events are associated with a coordination of firing in a majority of neocortical neurons. This was confirmed with dual intracellular recordings. Based on the amplitude that neocortical ripples reach during paroxysmal events, we propose a mechanism by which neocortical ripples during normal network activity could actively participate in the initiation of seizures on reaching a certain threshold amplitude. This mechanism involves a vicious feedback loop in which very fast oscillations in field potentials are a reflection of synchronous action potentials, and in turn, these oscillations help generate and synchronize action potentials in adjacent neurons through electrical interactions.

COMMENTARY

Considerable interest has been focused recently on the role of neuronal oscillations in normal and abnormal brain function, and the hypothetical role of fast oscillations in the generation of epileptic seizures continues to be a topic of intense research. Most attention has been directed at whether high-frequency oscillations—or “fast ripples” (80–500 Hz, often >200 Hz)—are important in seizure onset, and at the hypothetical mechanisms responsible for them. The main lines of investigation have involved electrophysiologic recordings of seizures or epileptiform activity from animal models and/or computer modeling of cortical networks. In this article, Grenier et al. used simultaneous intracellular and extracellular recordings during ketamine-xylazine anesthesia to analyze fast oscillations in cat neocortex during seizures. The incorporation of both intra- and extracellular recording techniques and the use of recordings from multiple sites during spontaneous neocortical seizures provided evidence that these events occur at the onset of most seizures, and that they arise from synchronous action potentials.

Much of the previous work in this field either has studied recordings of actual epileptic seizures in unanesthetized animals or humans, or has analyzed short-term induced epileptiform activity in brain slices from normal animals. Although the former studies have described actual epileptic seizures, these experiments have generally not been able to provide much insight into specific mechanisms. Although the latter experiments provided evidence concerning possible mechanisms, the work has often been based on forms of “hyperexcitability” that may not directly reproduce actual epileptic seizures. The work of Grenier et al. reports on a type of experimental *seizure* in an intact albeit anesthetized animal, and it provides further evidence that fast oscillations can occur at several periods during a seizure, but particularly at *seizure onset*. The simultaneous extra- and intracellular recordings show quite clearly that synchronous action potentials generate fast oscillations, and the authors discuss the possible mechanisms of neuronal synchronization.

In the early 1980s, experiments from several laboratories on hippocampal slices in solutions with reduced concentrations of extracellular calcium, which block action

potential-dependent transmission at chemical synapses, provided direct evidence that one or more electrical mechanisms contribute to the synchronization of action potentials during epileptiform activity. These studies generally showed that electrical field effects and/or gap junctions could synchronize action potentials and generate “population spikes”—events that appear equivalent to the fast oscillations seen in electrographic recordings. Because pyramidal cells far outnumber interneurons, and because the pyramidal cells have a parallel orientation, hippocampal and neocortical pyramidal cells are expected to dominate extracellular field-potential recordings from these structures. Thus, *electrical* communication between these projection neurons probably mediates—or at least contributes to—the synchronization of action potentials.

Several lines of evidence for the presence of gap junctions and electrotonic coupling between pyramidal cells have been advanced over the last two or three decades, but this hypothesis (and the data for it) remains controversial. Recent evidence actually suggests that *interneurons* may have substantially more gap junctions and more extensive electrotonic coupling than do pyramidal cells. Gap-junctional coupling among interneurons would potentially synchronize pyramidal cells, but it is difficult to understand how this mechanism would operate at a time scale fast enough to create fast oscillations. Gap junctions among pyramidal cells have been difficult to find unequivocally at the ultrastructural level, and immunohistochemical evidence from light microscopy lacks the resolution to identify gap junctions on specific neurons versus surrounding glial cells. If each pyramidal cell was connected by gap junctions to only a few of its neighboring pyramidal cells, such a neural network would be expected to fire synchronously when all or most of the neurons were depolarized near threshold, and would behave in a relatively asynchronous manner under most other conditions. Thus, the presence of only a few gap junctions over the surface of most pyramidal cells could potentially mediate the synchronization of action potentials

that appears to generate fast oscillations during spontaneous seizures.

Electrical field effects (or “ephaptic transmission”) involve synchronization of action potentials via current flow within a restricted extracellular space among parallel-oriented neurons. Numerous laboratories over the last 20 years have now confirmed that electrical field effects occur among synchronously active hippocampal pyramidal cells, but such interactions also may be present in the neocortex. Electrical field effects would presumably be much less effective in the neocortex than in the hippocampus, because of the many layers of neocortical neurons and the correspondingly smaller field potentials. Nonetheless, Grenier et al. showed that the fast oscillations could be more than a millivolt in amplitude, and such events would potentially depolarize adjacent silent neurons by several hundred microvolts. If these adjacent neurons were close to threshold for firing an action potential (e.g., from synaptic excitation), the electrical field effects could recruit adjacent neurons that would otherwise be silent. Thus, electrical field effects also may contribute to the synchronization observed during the electrographic seizures of cat neocortex associated with ketamine-xylazine anesthesia.

It is difficult to know now whether gap junctions, electrical field effects, or both mechanisms mediate the synchronization of action potentials that appears to generate the fast oscillations observed by Grenier et al. in cat neocortex under ketamine-xylazine anesthesia. It is interesting to speculate that both mechanisms might act synergistically during seizures. These events, however, are obviously a product of “normal” brain tissue versus tissue that has previously experienced chronic injury or that is genetically abnormal. Nonetheless, the mechanisms that contribute to synchronization could be enhanced in chronically epileptic tissue, and future research may discover how mechanisms of electrical communication operate in the epileptic brain.

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