

## FAST CORTICAL OSCILLATIONS ARE NOT DEPENDENT ON THE ACTIVITY OF GABAERGIC NEURONS

### Effects of Bicuculline Methiodide on Fast (>200 Hz) Electrical Oscillations in Rat Somatosensory Cortex

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Fast oscillatory activity (more than  $\sim 200$  Hz) has been attracting increasing attention regarding its possible role in both normal brain function and epileptogenesis, yet its underlying cellular mechanism remains poorly understood. Our prior investigation of the phenomenon in rat somatosensory cortex indicated that fast oscillations result from repetitive synaptic activation of cortical pyramidal cells originating from  $\gamma$ -aminobutyric acid (GABA)ergic interneurons (Jones et al., 2000). To test this hypothesis, the effects of topical application of the GABA<sub>A</sub> antagonist bicuculline methiodide (BMI) on fast oscillations were examined. At subconvulsive concentrations ( $\sim 10$   $\mu$ M), BMI application resulted in a pronounced enhancement of fast activity, in some trials, doubling the number of oscillatory cycles evoked by whisker stimulation. The amplitude and frequency of fast activity were not affected by BMI in a statistically significant fashion. At higher concentrations, BMI application resulted in the emergence of recurring spontaneous slow-wave discharges resembling interictal spikes (IISs) and the eventual onset of seizure. High-pass filtering of the IISs revealed that a burst of fast oscillations accompanied the spontaneous discharge. This activity was present in both the pre- and the postictal regimens, in which its morphology and spatial distribution were largely indistinguishable. These data indicate that fast cortical oscillations do not reflect GABAergic postsynaptic currents. An alternate account consistent with results observed to date is that this activity may instead arise from population spiking in pyramidal cells, possibly mediated by electrotonic coupling in a manner analogous to that underlying 200-Hz ripple in the hippocampus.

Additionally, fast oscillations occur within spontaneous epileptiform discharges. However, at least under the present experimental conditions, they do not appear to be a reliable predictor of seizure onset or an indicator of the seizure focus.

### COMMENTARY

Noninvasive recordings (electroencephalographic and magnetoencephalographic) of human somatosensory-evoked fast oscillations showed that they are of cortical origin (similar to the slow-wave components of the somatosensory evoked potential), and exhibit a somatotopic organization in the postcentral gyrus. The authors' previous work showed that rat somatosensory cortex fast oscillations were also of cortical origin, exhibiting a dipolar pattern in the lamina, which spread intracortically. Intracellular investigation found that whisker-evoked burst firing in fast spiking (FS) cells was closely associated with fast oscillations present in the surface record. Based on the supposition that these FS cells corresponded to the smooth or sparsely spiny  $\gamma$ -aminobutyric acid (GABA)ergic interneurons that have been identified by several groups, the authors suggested that inhibitory interneurons might act as the pacemakers of fast oscillations in neocortex. Thus the purpose of the present study was to elucidate the possible synaptic (i.e., GABA<sub>A</sub>ergic) contributions to fast oscillations in rat somatosensory cortex. The simple approach was to apply the GABA<sub>A</sub>ergic antagonist bicuculline methiodide (BMI) epicortically (in vivo), blocking this activity in the cortical network, while monitoring the effects on fast oscillatory activity.

The authors used both a low concentration of bicuculline (subthreshold for seizure generation), and a higher one (capable of provoking epileptiform activity), while generating fast oscillations by whisker stimulation. Epicortical application of bicuculline caused a significant increase in the number of oscillatory cycles evoked by whisker stimulation, but did not significantly affect the amplitude or frequency of this activity. Second, the spontaneous high-frequency oscillations that occurred within spontaneous epileptiform bursts were observed

when using doses of bicuculline sufficient to lead to seizure activity. Fast oscillations did not appear to be reliable indicators of interictal-to-ictal transition. The clear conclusion here is that fast cortical oscillations are not supported by fast GABA<sub>A</sub>ergic postsynaptic currents.

Rather, the authors argue, the neuronal element responsible for the dipolar field potentials is the pyramidal cells themselves, with their large apical dendrites. Pyramidal cells would thus serve as both pre- and postsynaptic elements in the fast oscillatory response with synchronized population firing imposing potent postsynaptic currents that regenerate the next cycle of fast activity and culminate as one peak of the fast oscillatory burst in field potentials. Because excitatory synaptic transmission could not support this high-fidelity system, and given previous computational studies of fast oscillations and previous experimental observations in the hippocampus, the

authors suggest that population spiking in pyramidal cells, possibly mediated by electrotonic coupling, would be the most parsimonious mechanism to support fast oscillations in somatosensory cortex.

An important theme that this study reinforces is that not all fast oscillations are mediated via GABA<sub>A</sub>ergic synapses (via inhibitory interneurons). A corollary to this is that not all fast spike waveforms recorded are mediated by fast spiking interneurons. Although the authors argue that continued study of these fast oscillations might contribute to understanding seizure initiation and propagation, their results showed fast activity was neither a reliable predictor of seizure onset nor a marker of the seizure focus.

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