Modeling of intracellular Ca2+ during epileptic seizures

Abstract

Considerable experimental evidence indicates that changes in cellular Ca^{2+} homeostatic mechanisms may be associated with changes in neuronal excitability and epileptogenesis. In these studies we look into various intracellular Ca^{2+} processes and investigate how they may influence the dynamics of repetitive bursting activities in simulated neuronal networks. Our results show that the process of Ca^{2+} clearance in neurons is an important factor influencing the dynamics of simulated bursting activity. Slow reduction in the rate of Ca^{2+} clearance produces changes in patterns of simulated EEG similar to those observed in ictal EEG recorded from humans. Synaptic potentiation produced by raised intracellular Ca^{2+} may be responsible for the late irregular bursting in both simulated EEG and in human EEG prior to seizure termination.

Introduction

Recent applications of time-frequency methods of signal analysis to intracranial recordings from humans with partial seizures reveal that ictal EEG in many patients share common characteristics. EEG during seizure include a period of rhythmic activity undergoing a monotonic decline in frequency and a following period of intermittent bursting before seizure termination (Franaszczuk et al. 1998). Mechanisms underlying these dynamical changes in EEG are poorly understood. Large neural network models are employed here to test the hypothesis that changes in intracellular calcium homeostasis may result in alteration of rhythmic activity similar to those seen in humans. These alterations include change in the pattern of periodic bursting due to changes in the intracellular calcium removal rate in pyramidal neurons, potentiation of calcium-dependent potassium conductance, and calcium related synaptic facilitation.

Methods

We utilize spatially distributed neural networks of single compartment neurons capable of reproducing synchronized bursting activity. Pyramidal cells in response to excitatory input fire repetitive bursts with a frequency dependent on calcium clearance rate. Interneurons respond to excitatory input with nonadapting spike train. Intracellular calcium dynamics is modeled in details including calcium influx and efflux, binding and diffusion, and uptake. The network is activated by random input. In order to simulate the repetitive rhythmic activity, the strengths of inhibitory synaptic weights are gradually decreased resulting in recurrent bursts in neurons in a network. The local field potential (LFP, modeled as an average membrane potential of all neurons in a network) was calculated and compared with ictal EEG from humans. For comparison with EEG a matching pursuit time frequency decomposition was used (Mallat and Zhang, 1993)

Results

In these neural network models, induced recurrent rhythmic activity results in higher than normal calcium influx into neurons, which slows the rate at which calcium is cleared from neurons. Decreasing the rate of calcium clearance from neurons results in a decreases of the frequency of synchronous bursts in simulated network activities. The time-frequency decompositions of simulated LFPs reveal prominent rhythms with a monotonic decline in frequency from 7.5 to 2.5 Hz (Fig. 1A). The patterns of changes of the frequency in simulated LFPs are consistent with the patterns of changes of the dominant frequency observed in recordings from depth electrode contacts nearest the region of mesial temporal seizure onset in humans (Fig. 1B). The dominant frequency of the simulated LFP is correlated with the value of the calcium clearance rate. In this model the raised level of Ca^{2+} in neurons produces synaptic potentiation which later lead to irregular bursting. A similar pattern is observed in human EEG prior to seizure termination.

Conclusions

Identifying potential mechanisms underlying the dynamic changes seen in epileptogenic activity in large neural networks can yield important insights into seizure evolution and termination. The neural network models studied here allow one to modify cellular characteristics to understand what changes at the cellular level could produce the network behavior observed during seizures. Based on the described saturation in calcium removal mechanisms and synaptic potentiation, these network models can reproduce characteristics of the repetitive synchronous neuronal bursting that are consistent with patterns of organized rhythmic activity occurring in seizures of mesial temporal lobe onset. These results also provide insights into potential mechanisms of seizure termination.

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References

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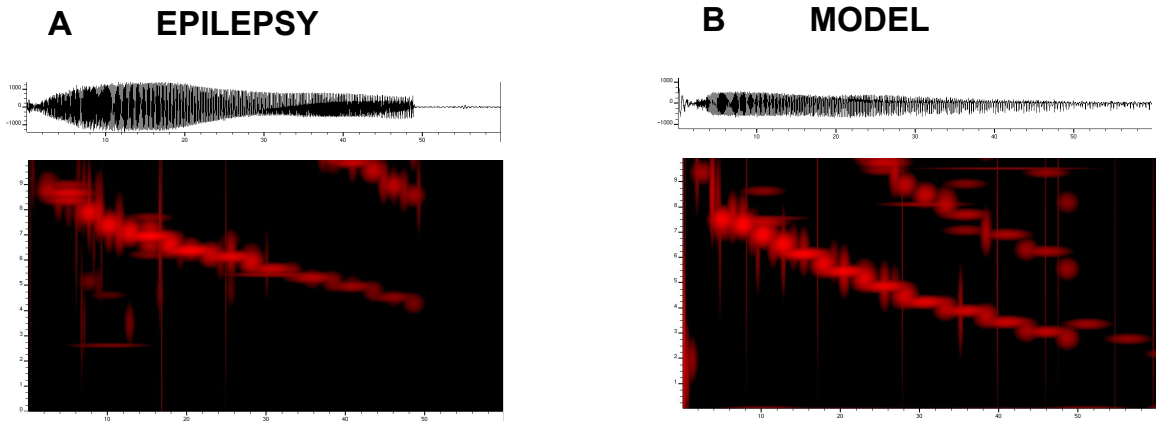

Figure 1 (A) Time-frequency energy distributions maps (lower panels) of EEG signals (upper panels) from depth electrode contacts nearest the mesial temporal regions of seizure onset in humans during the period of organized rhythmic activity. (B) Time-frequency distribution (lower panel) of simulated local field potential (upper pannel) Both EEG and LFP signals were band-filtered (2-10 Hz) prior to time-frequency decomposition to separate the predominant frequency.