

Computational analysis of the factors contributing to post-traumatic network hyperexcitability in the dentate gyrus.

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Head injury is a major risk factor in the etiology of temporal lobe epilepsy (TLE). Studies using a rodent model of concussive head trauma have identified specific patterns of cell loss and synaptic reorganization in the dentate gyrus after brain injury, which are similar to the changes in human TLE. However, the contribution of each of these cellular and synaptic alterations to increased excitability in the dentate neuronal circuits is not known. The objective of this study is to determine the factors critical to post-traumatic dentate hyperexcitability by independently simulating the loss of specific populations of hilar neurons, changes in interneuronal activity and the abnormal recurrent granule cell connections in a network model of the dentate gyrus.

As the first step in designing the dentate network, we have developed multi-compartmental models of excitatory cell types in the dentate gyrus. Here we present the computational models of dentate granule cells and mossy cells. Simulations were performed using NEURON (Hines 1993). The active conductances in the model cells included fast sodium, fast delayed rectifier potassium, A-type potassium, large and small conductance calcium-dependent potassium and L- and N-type of calcium channels. Additionally, slow delayed rectifier potassium and T-type calcium channels were included in the granule cell. The granule cell had four functionally distinct compartments with different densities of active channels. The model mossy cell had four dendrites each with four distinct compartments coupled to the soma and contained the H-channel in addition to the channels listed above. The active conductances were distributed uniformly in the dendritic compartments of the mossy cell. Correction for the spine morphologies was included in both cell types. The passive parameters of the model cells were fitted to the membrane properties from experimental data in control animals. The action potential threshold, spike frequency adaptation, fast and slow afterhyperpolarization and firing frequency of the model cells were similar to the corresponding biological neurons.

We expect that the dentate neuronal network built from multi-compartmental models that reflect the active properties of the excitatory and inhibitory cell types would provide a novel approach to identify the network parameters critical to post-injury dentate hyperexcitability.

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