Modeling How the Decrease in Sodium Channel Density of Inhibitory Cells in Epileptic Patients Affects Neuronal Oscillations

Vinita Saxena1, 3, Elizabeth Rosenthal2, 3, Dr. Marianne Bezaire3
Davis Senior High School, Davis, CA1; The Brearley School, New York, NY2; Boston University, Boston, MA3

Introduction

- Patients with epilepsy are prone to repeated epileptic seizures, which are defined by the spontaneous excitation of neurons.1
- Two to five percent of the world’s population experiences at least one seizure, and one third of those people develop epilepsy.2
- The exact causes of epilepsy are currently unknown, although many hypotheses are being tested.
- There may be mutations in genes that code for NaV1.1, a voltage-gated sodium channel found in inhibitory cells. There is a correlation between the number of damaged sodium channels and the severity of each epilepsy case.3
- Sodium channels help generate an action potential, the electrical signal that is propagated down the neuron’s axon. Neurons fire when their negatively charged axon becomes more positive due to sodium ions entering the cell. The more open sodium channels there are, the more positive the cell can get and the more likely it is to fire.
- Inhibitory cells make other neurons less likely to fire, while excitatory cells make other neurons more likely to fire.
- In order to mimic the damaged sodium channels found in some epileptic patients, we modeled excitatory and inhibitory neurons and decreased the number of sodium channels on the inhibitory cell. We used DynaSim, a graphical user interface created for MATLAB, a programming language. Our goal was to investigate the change in firing rate of each cell type to further relate sodium channel density to epilepsy.

Methods

- This simulation was run using MATLAB R2017b and DynaSim.
- The network contained 200 excitatory cells and 20 inhibitory cells connected to each other.4
- The only variable was the density of sodium channels on the inhibitory cells, which started at 120 nanosiemens/cm² and decreased by tens until it reached 10 nanosiemens/cm².5
- The parameters were set with DynaSim’s default values for the simplified Hodgkin and Huxley cell model.6
- The simulations ran for 1,000 milliseconds with a time step of 0.01 milliseconds.
- To validate the model, the amount of excitatory and inhibitory cells changed multiple times, which led to the spike rate appropriately differing each time.

Results

As shown by the following graphs, the firing rate of the excitatory cells increased as the sodium channel density decreased.

Discussion

Conclusions:
- There was an increase in the firing rate of the excitatory neurons when there were fewer sodium channels on the inhibitory cells because it was more difficult for the inhibitory cells to get positive enough to fire. Thus, with less inhibition, the excitatory cells were able to fire more frequently.
- This model represented excitatory and inhibitory neurons in the brain, and the results of the simulation demonstrate that decreasing sodium channel density could cause epilepsy.

Caveats:
- Our model was a simplified version of the brain which only consisted of two cell types, excitatory and inhibitory, and also lacked randomness.

Future Directions:
- To counteract the increased firing rate of excitatory neurons, future simulations could decrease the density of NaV1.6, sodium channels found in excitatory cells.3 This could cause the excitatory cells to fire less frequently despite their lack of inhibition.
- Other models could test the effects of increasing the weight of the gamma-aminobutyric acid (GABA) synapse affects the neuronal activity.
- The GABA synapse is an inhibitory synapse, so increasing the synaptic weight could cause the excitatory cells to have more inhibition even when the inhibitory cells are firing less often.
- These simulations could provide testable predictions for experimentalists and lead to the development of medications that target NaV1.6 channels or GABA synapses.1

References


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