Study of the mechanisms of hippocampal epileptogenesis through computational modeling

PhD thesis - summary

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Epilepsy is one of the most frequent neurological diseases, having important effect on the quality of life of the patient and a severe socio-economic impact.

In spite of the huge intellectual and financial effort in the research of new diagnostic, treatment and prevention methods in epilepsy, the details of several important aspects of epileptogenesis is not fully known yet. Thus the treatment of epilepsy is limited to the prevention of the seizures, being more anti-ictal than anti-epileptic. This project proposed to study the relationship between the modifications of the neural networks and epileptogenesis. This study focused on the modifications of the CA1 region of the hippocampus as the last step of information processing in the hippocampus.

The working hypothesis is that the modifications of interneuronal connections, together with the increased number of gap junctions can modify the operation of the hippocampal circuit leading to epileptic seizures.

The aim of the project was the study of the mechanisms of epileptogenesis through computational modeling and the study of the functional consequences caused by the anatomical changes described in the literature.

Simulations were performed with the program Neuron (version 7.2), freely accessible on the internet.

The thesis consists of four studies.

1. Modeling the dependence of the somatic postsynaptic potential amplitude on the position of the synapse in hippocampal pyramidal cells

In this part we examined the necessary degree of complexity of the models to reproduce the main features of synaptic integration. Our studies show that the two main excitatory

synaptic inputs (through Schaffer collaterals and the perforant path) contribute with a different degree to the output of the neuron. This is caused by the geometry of the CA1 pyramidal neuron, having an apical dendritic tree that spreads on a 0.5-1 mm distance, with several thin dendritic branches, and by the varying distribution of the ionic channels on the dendritic tree.

Our conclusion is that for the synaptic integration of the CA1 pyramidal cell the dendritic tree should be modeled, thus the model cannot be reduced to a monocompartmental one. The synaptic inputs through Schaffer collaterals and the perforant path are integrated in a different manner, thus they have to be modeled separately.

2. Comparison of the published compartmental models of CA1 pyramidal cells

We studied 22 computational models of CA1 pyramidal cells published on the internet. We compared the geometry, passive properties, the distribution of ion channels and the formulas describing the active conductances. Based on the similarities and differences in the distribution and kinetics of ion channels, and also considering the complexity of the modes, we chose five models to examine the electrophysiological properties.

Our study shows an important heterogeneity among the studied models. Thus the electrophysiological properties of the models vary with the geometry of the modeled cells, but more important is the effect of the differences in the active membrane properties.

3. Development of a simplified model of the CA1 pyramidal cells

The geometry of the studied models is realistic, they contain more than one hundred compartments, and a large number of active conductances are implemented having non-uniform distribution. Because of the large computational cost of these models we proposed to develop a simplified model which reproduces the main electrophzsiological properties of the CA1 pyramidal cells.

Our model has simplified geometry and a relatively small number of active conductances. The model reproduces the main features of the firing pattern and backpropagating action potentials described in the literature with a low computational cost, thus the model is suitable to be used in a larger (several hundred cells) model of the CA1 neural network.

4. Study of several factors involved in epileptogenesis

We studied the mechanisms which can induce high frequency oscillations and contribute to the recruitment of new neurons in the oscillation. We used modified version of a validated model which reproduces memory storage and recall, physiological processes of the hippocampus. We studied the effect of mechanisms assigned to epileptogenesis.

The network with reduced dendritic inhibition together with the insertion of gap junctions generated an extracellular signal with signs of epileptic activity, high frequency oscillations, reduced theta activity and the spread of activity to almost all pyramidal cells.

The novelty of our study is that the network used for the simulations was not developed to reproduce the epileptic activity, but originally shows the physiological properties of the hippocampus of memory formation and recall.