A modelling study of beta-amyloid induced change in hippocampal theta rhythm

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Summary: Many dementia cases, such as Alzheimer's disease (AD), are characterized by an increase in low frequency field potential oscillations. However, a definitive understanding of the effects of the β-Amyloid (Aβ) peptide, which is a main marker of AD, on the low frequency theta rhythm (4-7Hz) is still unavailable. In this work, we investigate the neural mechanisms associated with Aβ toxicity using a conductance-based neuronal network model of the hippocampus CA1 region. We simulate the effects of Aβ on the A-type fast-inactivating K^+ channel by modulating the maximum conductance of the current in pyramidal cells, denoted by g_A. Our simulation results demonstrate that as g_A decreases (through Aβ blockage), the theta band power first increases then decreases. Thus there exists a value of g_A that maximizes the theta band power. The neuronal and network mechanism underlying the change in theta rhythm is systematically analyzed. We show that the increase in theta power is due to the improved synchronization of pyramidal neurons, and the theta decrease is induced by the faster depolarisation of pyramidal neurons.

Method: The network model consists of 10 pyramidal, 30 OLM, 100 basket and 50 MSGABA Hodgkin-Huxley like neurons. Synapses are mediated by NMDA, AMPA and $GABA_A$. The effect of Aβ on the A-type current of pyramidal cell is simulated by reducing the g_A and the subsequent theta rhythm power spectrum is evaluated. The synchronization property of pyramidal cells is investigated using an uncoupled pyramidal neuron model with only the A-type, leak, Na^+ and delayed-rectifier K^+ currents and a phase plane analysis. The whole network is used to systematically study the mechanism of decreasing theta with very low g_A. The analysis is performed in a noise free condition.

Results and conclusions: We find that the increase in theta band power is due to the improved synchronization among the pyramidal cells. For normal g_A (control condition), a stable fixed point (through a saddle-node bifurcation) reduces the excitability of pyramidal cells because the tendency to spike depends on the initial state. Thus, these cells are less synchronous in the presence of noise. For moderately lower g_A, only a limit cycle appears, which improves the synchronicity, therefore the theta band power enhances. When the g_A is further decreased below a critical point, the theta oscillation abruptly disappears. Within a theta period, the pyramidal cells spike first and the OLM cells also spike in phase. After the spikes of OLM, both the pyramidal and basket cells start to depolarize. As the basket cells depolarize faster than the pyramidal cells, the basket cells will spike first and inhibit the pyramidal cells. During the spiking of basket cells, MSGABA cells gradually depolarize and finally start spiking, which inhibit basket cells. However, when g_A is sufficiently low, the pyramidal cells will depolarize faster than the basket cells. This results in an earlier spike than that of basket cells. As a result, the basket cells will be inhibited and the pyramidal cells will be able to continuously spike at a higher frequency than theta. Our simulation study and analysis predict that the change in theta rhythm in AD is dependent on the concentration of Aβ (via A-current blockage) in the hippocampus CA1 region, which can be verified in experiments. The details of the network model and analysis will be presented in a full paper to be submitted soon.

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