PROGRESSIVE EFFECT OF BETA AMYLOID PROTEIN ACCUMULATION ON THE FIRING PROPERTIES OF CA1 PYRAMIDAL NEURONS: A MODEL STUDY SUGGESTING A POSSIBLE TREATMENT

M. Migliore, V. Culmone

Institute of Biophysics, National Research Council, Palermo, Italy

Accumulation of β-Amyloid (Aβ) peptide is a characteristic hallmark of Alzheimer's disease (AD) and it could be one of the major causes for neuronal degeneration and death. In spite of the intense experimental work to explain the possible underlying mechanisms of action, many important details are missed. Part of the problem might be that several independent studies demonstrated as Aβ may affect the normal activity of a neuron in opposite ways, making a neuron more excitable (by reducing the A-type or the DR K+ current) or less excitable (by reducing synaptic transmission and Na+ current). The interplay of these mechanisms makes thus difficult to link individual experimental findings with the more general problem of understanding the progression of the disease. This is an important issue, especially for the development of new drugs. In the present study, we used a realistic model of a hippocampal CA1 pyramidal neuron to implement the possible pathological consequences of Aβ when it affects more and more neuronal membrane area. The intrinsic electrical membrane and synaptic properties were progressively modified, taking into account multiple and different experimental findings, to study the spike probability of a neuron at different stages of the disease. The results show that the overall effect of the Aβ is to progressively reduce cell’s excitability, with larger effects for an intermediate range of synaptic inputs strength. The model predicts a possible therapeutic intervention, suggesting how and which mechanism can be targeted by a drug to restore the original conditions.