

Early alteration of hippocampal neuronal firing induced by Abeta42 oligomers in Alzheimer's Disease

Department of Drug Science and Technology, Torino University Corso Raffaello 30 10125, Torino (Italy)

Andrea Marcantoni¹, Arianna Allio¹, Chiara Calorio¹, Daniela Gavello¹, Piergiorgio Montarolo², H. Marie³, Emilio Carbone¹

1) *Department of Drug Science and Technology, Torino University, Torino, Italy*

2) *Department of Neuroscience, Torino University, Torino, Italy*

3) *Institut de Pharmacologie Moléculaire et Cellulaire (IPMC), CNRS (UMR7275), Valbonne, France*

Among the various hallmarks of Alzheimer's Disease (AD), the activation process of the amyloid-cascade is one of the most studied. It assumes that the accumulation of oligomers of Amyloid Beta peptides (Abeta), produced by the proteolytic processing of the amyloid precursor protein (APP) is the initiating event that triggers the progressive dismantling of the synapses, neuronal circuits and networks. However, so far there are not yet clear data regarding any possible Abeta-induced impairment of neuronal excitability.

Our previous results indicate that in Tg2576 mice neurons from Lateral Entorhinal Cortex (LEC) are characterized by early impairments of their excitable profile. Tg2576 mice are characterized by overproduction of different Abeta peptides, like Abeta40, Abeta42, Abeta*56 and exhibit hyperphosphorylated tau. These considerations suggest that any difference between WT and Tg2576 mice on neuronal function cannot be related to a precise cause. To address this issue, here we propose to test the effects of Abeta42 on Ca²⁺ dependent excitability profile of hippocampal neurons from WT embryonic mice. This peptide is known to be able to induce severe and permanent changes of synaptic functions. Our preliminary experiments on cultured hippocampal networks reveal that pre-incubation of neurons with Abeta42 oligomers increases intracellular Ca²⁺ concentration (measured by Ca²⁺ fluorescence microscopy). This effect is accompanied by a paradoxical firing inhibition. The study of the cause of the Abeta42 dependent Ca²⁺ dyshomeostasis let us to conclude that both ryanodine (RYRs) and NMDA receptors (NMDARs) function is altered. When we focused on hippocampal network excitability, we indicated RYRs as the main target of Abeta42, being their inhibition followed by a (partial) recovery of both firing frequency and synchronism. We also found that incubation of the BK channels inhibitor paxilline with Abeta42 oligomers revert the oligomers-induced inhibition of firing activity, thus indicating that BK channels may be a possible early target of AD. Finally, the block of NMDA receptors is followed by an increased firing synchronization, but a decreased firing frequency.

In conclusion, by focusing on the Abeta42 dependent early effects on Ca²⁺ dependent neuronal excitability, we identified three main direct or indirect targets represented by RYRs, NMDARs and BK channels. Accordingly to previous reports, we further indicate RYRs as critically involved in AD development. Their inhibition may in turn be useful for identifying effective therapies that could enhance the quality of life of AD patients.