

## C-JUN N-TERMINAL KINASE REGULATES THE FIRST EVENTS OF SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive impairment due to alterations of the synaptic functions. The synaptic dysfunction seems to be caused by amyloid beta ( $A\beta$ ) oligomers. To investigate the molecular mechanisms by which  $A\beta$  oligomers may induce synaptic degeneration we characterized an in vitro model of synaptic dysfunction. Hippocampal neurons from Brainbow mice were treated with sub-toxic concentrations of  $A\beta$  (1-42) synthetic oligomers in order to induce the early events that lead to synaptic dysfunction. Brainbow mice expressing the yellow fluorescent protein (YFP) specifically in neurons were used to analyse changes in the morphology and the number of spines in vitro in physiological conditions, without need of infection or transfection of exogenous molecules. Following sub-toxic  $A\beta$  exposures we observed a reduction of the number of spines and a decrease of post-synaptic markers (PSD95, drebrin and NMDAR). In these conditions the c-jun N terminal kinase (JNK) was activated indicating its role in the intracellular mechanisms that regulate the dysfunction of dendritic spines. Interestingly, PSD95, an important indicator of synaptic integrity and function, is a target of JNK. Thus, we tested the possibility that inhibition of JNK, with the specific cell permeable peptide D-JNKI1, could prevent the synaptic degeneration induced by  $A\beta$  oligomers. In preliminary results D-JNKI1 reverted the  $A\beta$  induced loss of PSD95 in the membrane.

Our data indicate the involvement of the JNK signalling pathway in  $A\beta$  induced synaptic dysfunction. Inhibition of this pathway with D-JNKI1 could be a promising tool to delay AD.