JNK mediates synaptic dysfunction caused by Aß oligomers in Alzheimer disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that begins with episodic short-term memory deficits and culminates with cognitive impairment and memory loss. The first signs of memory loss are due to synaptic dysfunction, which is triggered by soluble toxic oligomeric assemblies of ß-amyloid peptides (Aß).
The molecular mechanisms underlying the synaptic injury remain unclear, but there are increasing evidences of the involvement of mitogen-activated protein kinases (MAPKs). Among these enzymes, c-jun N-terminal kinase (JNK) has been extensively studied for its role in AD pathology. To have a deeper insight of the ole played by this kinase we set up a new *in vitro* model of synaptic degeneration following exposure of hippocampal neurons from Brainbow mice with sub-toxic concentrations of synthetic Aß oligomers. Abeta oligomers caused a strong activation of the JNK pathway in the synaptic compartment. This correlated with the reduction of dendritic spines density, the decrease of postsynaptic markers (AMPAR and NMDAR subunits, PSD95 and drebrin) and the activation of caspase-3 in the postsynaptic compartment. To confirm the involvement of JNK in synaptic degeneration mechanisms induced by Aß oligomers, we used the specific cell permeable JNK inhibitor peptide, D-JNKI1. Treatment with D-JNKI1 reverted the synaptic degeneration by preventing the loss of dendritic spines and the reduction of AMPA-R and NMDA-R subunits, PSD95 and drebrin from the postsynaptic membrane. D-JNKI1 treatment prevented caspase-3 activation as well.
These results were confirmed in vivo studies with an AD mouse model. In the hippocampus of TgCRND8 mice, JNK is activated in the postsynaptic compartment before the onset of the cognitive impairment. To characterize the role of JNK in vivo we treated TgCRND8 mice with D-JNKI1. D-JNKI1 treatment prevented the loss of postsynaptic proteins and glutamate receptors from the postsynaptic density and the reduction in the size of excitatory synapses as revealed by quantitative electron-microscopy analysis.
This observations unveil that JNK plays a crucial role in the onset and progression of synaptopathy and that its specific inhibition offers an innovative therapeutic strategy to prevent spine degeneration in Alzheimer disease.
Noteworthy, the efficacy of the inhibitor D-JNKI1 shows the existance of new therapeutic targets and opens opportunities for the development of innovative approaches to prevent synaptopathy. These observations may have important significant ,implications in other neurodegenerative diseases such as Parkinson's, Huntington's, Prion disease, Schizophrenia, Autism and Rett Syndrome, which are characterized by synaptopathy in their early stage as well.