NICOTINE PREVENTS SYNAPTIC IMPAIRMENT INDUCED BY Aβ OLIGOMERS THROUGH A7-NACHR ACTIVATION

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Introduction: An emerging view on Alzheimer disease's (AD) pathogenesis considers amyloid-β (Aβ) oligomers as a key factor in synaptic impairment and rodent spatial memory decline. Alterations of the α7-nicotinic acetylcholine receptor (nAChR) have been implicated in AD pathology. Activation of α7-nAChR by nicotine improves spatial memory and enhances hippocampal synaptic transmission. However, it is unknown whether nicotine can improve the memory impairment and synaptic failures induced by Aβ oligomers.

Aims: To determine whether activation of α7-nAChR by nicotine has a neuroprotective effect against Aβ oligomers-induced damage.

Methods: For in vivo assays, we treated with nicotine to double transgenic APPswe/PSEN1DE9 (APP/PS1) mice and we analyzed spatial memory using the Morris Water Maze test. For in vitro assays, we analyzed the expression and distribution of synaptic proteins in hippocampal neurons exposed to Aβ oligomers, nicotine and α7-nAChR inhibitors.

Results: We found that chronic treatment with nicotine prevents memory deficit in young and old APP/PS1 transgenic mice. Also, nicotine protects from synaptic and morphological impairments induced by Aβ oligomers through α7-nAChR activation, in hippocampal neurons. Nicotine prevents both, early post-synaptic impairment and later pre-synaptic damage induced by Aβ oligomers. Interestingly, the effect of nicotine is blocked by wortmannin (WT), an inhibitor of the phosphatidylinositol-3-kinase (PI3K) pathway, suggesting that the PI3K/Akt pathway plays a major role in the nicotine neuroprotective effect.

Conclusion: Our results demonstrate that nicotine prevents memory deficit and synaptic impairment induced by Aβ oligomers. Activation of the α7-nAChR/PI3K pathway could be a therapeutic target for AD treatment.

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