



# Antiamnesic and Neuroprotective Effects of the Aminotetrahydrofuran Derivative ANAVEX1-41 Against Amyloid $\beta_{25-35}$ -Induced Toxicity in Mice

## Abstract

The anti-amnesic and neuroprotective activities of the new aminotetrahydrofuran derivative tetrahydro-*N,N*-dimethyl-5,5-diphenyl-3-furanmethanamine hydrochloride (ANAVEX1-41), a nonselective muscarinic receptor ligand and  $\sigma_1$  protein activator, were examined in mice injected intracerebroventricularly with amyloid  $\beta_{25-35}$  ( $A\beta_{25-35}$ ) peptide (9 nmol).  $A\beta_{25-35}$  impaired significantly spontaneous alternation performance, a spatial working memory, and passive avoidance response. When ANAVEX1-41 (1–1000  $\mu\text{g}/\text{kg}$  i.p.) was administered 7 days after  $A\beta_{25-35}$ , ie, 20 min before the behavioral tests, it significantly reversed the  $A\beta_{25-35}$ -induced deficits, the most active doses being in the 3–100  $\mu\text{g}/\text{kg}$  range. When the compound was preadministered 20 min before  $A\beta_{25-35}$ , ie, 7 days before the tests, it prevented the learning impairments at 30–100  $\mu\text{g}/\text{kg}$ . Morphological analysis of corticolimbic structures showed that  $A\beta_{25-35}$  induced a significant cell loss in the CA1 pyramidal cell layer of the hippocampus that was prevented by ANAVEX1-41 (100  $\mu\text{g}/\text{kg}$ ). Increased number of glial fibrillary acidic protein immunopositive cells in the retrosplenial cortex or throughout the hippocampus revealed an  $A\beta_{25-35}$ -induced inflammation that was prevented by ANAVEX1-41. The drug also prevented the parameters of  $A\beta_{25-35}$ -induced oxidative stress measured in hippocampus extracts, ie, the increases in lipid peroxidation and protein nitration. ANAVEX1-41, however, failed to prevent  $A\beta_{25-35}$ -induced caspase-9 expression. The compound also blocked the  $A\beta_{25-35}$ -induced caspase-3 expression, a marker of apoptosis. Both the muscarinic antagonist scopolamine and the  $\sigma_1$  protein inactivator BD1047 prevented the beneficial effects of ANAVEX1-41 (30 or 100  $\mu\text{g}/\text{kg}$ ) against  $A\beta_{25-35}$ -induced learning impairments, suggesting that muscarinic and  $\sigma_1$  targets are involved in the drug effect. A synergic effect could indeed account for the very low active doses measured *in vivo*. These data outline the therapeutic potential of ANAVEX1-41 as a neuroprotective agent in Alzheimer's disease.

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