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ANTI-AMNESTIC AND NEUROPROTECTIVE ACTIVITIES OF ANAVEX2-73: A NEW AMINOTETRAIHYDROFURAN DERIVATIVE ACTING AS A MIXED MUSCARINIC/SIGMA-1 LIGAND, IN PHARMACOLOGICAL AM) PATHOLOGICAL MODELS OF AMNESIA

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Background: Tetrahydro-N,N-Mmethyl-2,2diphenyl -furanmethanamine (ANAVEX2-73) is a new sigma-1 receptor (SIR) ligand, with a sur-micro-molar affinity (IC50= 860 Nm & Xc Ki= 710 nm) and low affinities (IC50=3.3-5.2μM) for M I -M4 muscarinic receptors. No affinity was found for sigma-2 receptors. Methods: The anti-amnesic abilities of ANAVEX2-73 were examined in severed models of pharmacological and pathological amnesia in mice submitted to a short-term and long-term memory test, spontaneous alternation and passive avoidance, respectively. Results: The compound failed to affect the learning abilities alone, but reversed in a bell-shaped manner the deficits induced by the M1 muscarinic antagonist scopolamine, the NMDA receptor antagonist dizocilpine, or the central injection of amyloid beta(25- 35)-peptide(Ab25-35), a nontransgenic mouse model of Alzheimer's disease (AD). These effects were blocked by a pre-injection of the SIR antagonist BDI047, confining an action at SIR sites. Moreover, we examined the neuro-protective effects of ANAVEN2-73 in Ab-treated mice. Central injection of Ab25-35 into the mouse brain induces within 7 days histological and biochemical changes, oxidative stress and learning deficits. Injection of scrambled Ab peptide was used as control. ANAVEX2-73 was injected once, 20 min before Ab25-35 and 7 days before the behavioral tests and biochemical analyses. ANAVEX2-73 dose-dependently prevented the appearance of Ab25-35-induced learning deficits, at 30- 1000 μg/kg, the same dose-range as observed for acute anti-amnesic effects. ANAVEX27-3 prevented the Ab25-35-induced increase in lipid peroxidation and caspase-3 expression in the hippocampus. Conclusions: The neuroprotective effects at the behavioral and biochemical levels were differentially sensitive to pre-treatments with either BD1047 or scopolamine, indicating a mixed mechanism of action involving S1R and muscarinic systems.

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