

## Neuroprotective effects of activators/agonists of the sigma-1 chaperone protein against amyloid toxicity in a mouse model

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The previously named 'sigma-1 ( $\sigma_1$ ) receptor' is a chaperone protein located on the endoplasmic reticulum (ER) membrane, precisely at focal contacts between the ER and mitochondria (Hayashi & Su, Cell 131:596, 2007). The protein regulates the activity of different ER proteins, like IP<sub>3</sub> receptors or ER stress sensors (GRP78/BiP, PERK, ATF-6). The  $\sigma_1$  chaperone has the unique particularity to be sensitive to synthetic ligands, which therefore allow a very focal regulation of intracellular calcium homeostasis at ER and/or mitochondria contacts. As a consequence,  $\sigma_1$  activators/agonists have been shown to induce acute modulation of transduction pathways, effective at the behavioral level.  $\sigma_1$  Activators are indeed anti-amnesic, antidepressant and neuroprotective compounds. We validate new  $\sigma_1$  activator compounds as neuroprotective agents against amyloid toxicity and analyze their mechanism of action. PRE-084 is a morpholine piperidine derivative acting as a high affinity and selective  $\sigma_1$  activator. ANAVEX1-41 is a tetrahydro-furanmethanamine that shows high affinity for M1, M2, M4 muscarinic acetylcholine receptors and  $\sigma_1$  protein. Both compounds are potent anti-amnesic drugs alleviating learning impairments observed in mice after the central (i.c.v.) injection of amyloid  $\beta$ 25-35 peptide (A $\beta$ 25-35). Central administration of A $\beta$ 25-35 induces within one week histological and biochemical changes, memory deficits, oxidative stress and ER stress in sensitive brain structures (hippocampus, cortex), highly reminiscent of the amyloid toxicity observed in Alzheimer's disease. A $\beta$ 25-35 also provokes the induction of intracellular pro-apoptotic caspases and Bax-related proteins, markers of the induction of apoptosis. At the morphological level, A $\beta$ 25-35 induces a marked glial (astroglia, microglia) reaction and cell loss quantifiable in pyramidal layers of the hippocampus. Pre-administration of PRE-084 or ANAVEX1-41 prevents significantly all these pathological changes, showing that  $\sigma_1$  activators are effective neuroprotectants. Part of the mechanism involves regulation of the expression of activity of IP<sub>3</sub> receptors or ER stress sensors, in relation with the massive calcium overload induced by A $\beta$ 25-35. Moreover, ANAVEX1-41 is active in 30-100  $\mu$ g/kg i.p. dose-range, suggesting a cooperative action between muscarinic and  $\sigma_1$  targets.