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A NOVEL MULTIPOTENT SIGMA 1/M1 MUSCARINIC ACTIVATOR FOR A COMPREHENSIVE THERAPEUTIC STRATEGY IN ALZHEIMER'S DISEASE

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The M1 muscarinic agonists AF102B (Evoxac: prescribed in Sjogren's syndrome, SjS) and AF267B (effective in SjS) are cognitive enhancers and disease modifiers. Notably, i) AF102B decreased CSF Abeta in Alzheimer's disease (AD) patients (Nitsch et al, 2000); ii) AF267B was effective against cognitive deficits, Abeta42 and tau pathologies in 3xTg-AD mice (Caccamo et al, 2006); and iii) AF102B and AF267B decreased brain alpha-synuclein in transgenic mice overexpressing human alpha-synuclein (Fisher et al, ADPD2011). Thus M1 muscarinic agonists can alter pathologies in AD, Parkinson's disease and Lewy body dementia. We have further hypothesized that synchronized activation of the M1 muscarinic receptor (M1mAChR) and the molecular chaperone sigma-1 receptor (Sig1R) may have broader therapeutic benefits. To achieve this goal, we designed AF710B (MW 357.5) which shows a novel mechanism of action (MoA) via selective Sig1R activation and M1 muscarinic allosteric modulation, but not resembling sigma1, M1 allosteric or orthosteric and sigma1/M1 agonists, respectively. AF710B (nM range, in vitro) decreased Abeta, Tau-hyperphosphorylation, GSK3beta activation, and prevented apoptosis and mitochondrial dysfunction via increased Bcl2/Bax. AF710B is a highly potent cognitive enhancer (rats: 1-30 and 10-100 mcg/kg, po in trihexyphenidyl- and MK801-induced passive avoidance impairments, respectively). AF710B is devoid of side effects, having an unprecedented safety margin (> 50,000; po). Furthermore, in female 3xTg-AD mice AF710B (10 mcg/kg, ip/daily for 2 months) – i) mitigated cognitive impairments in Morris water maze; ii) decreased BACE1, GSK3beta activity, p25CDK5, inflammation, soluble and insoluble Abeta40, Abeta42, plaques and tau pathologies.

Conclusions: The MoA of AF710B involves a super-sensitization of M1mAChR through a hypothetical heteromerization with Sig1R. AF710B is highly efficacious against the major AD hallmarks (e.g. cognitive deficits, amyloid and tau pathologies, inflammation and mitochondrial dysfunctions). This indicates therapeutic advantages for AF710B in AD and other protein-aggregation diseases vs. a plethora of experimental and licensed treatments.

Keywords: sigma1 agonists; m1 muscarinic; allosteric; AD