M1 muscarinic agonists and a multipotent activator of sigma1/M1 muscarinic receptors: Future therapeutics of Alzheimer's disease (AD)

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Activation of the M1 muscarinic receptor (M1mAChR) may be beneficial against cognitive deficits and pathologies of Alzheimer's disease (AD) and therefore M1 muscarinic agonists are considered rational treatment strategies. We have further hypothesized that synchronized activation of the M1mAChR and the molecular chaperone sigma-1 receptor (Sig1R) may have broader therapeutic benefits.

The M1 selective muscarinic orthosteric agonists AF102B (Evoxac: prescribed in Sjogren's syndrome), AF267B, AF292 and AF710B (MW 357.5), which targets both the M1mAChR and Sig1R, were tested in vitro and in several animal models for AD. These compounds are cognitive enhancers and disease modifiers in vitro and in vivo. Notably, i) AF102B and AF267B decreased CSF Abeta levels in preclinical studies (Beach et al, 2001); ii) AF267B was effective against cognitive deficits, Abeta42 and tau pathologies in 3xTg-AD mice (Caccamo et al, 2006); iii) AF102B and AF267B decreased brain alpha-synuclein in transgenic mice overexpressing human alpha-synuclein (Fisher et al, ADPD2011); and iv) AF102B decreased CSF Abeta in AD patients (Nitsch et al, 2000). AF710B (nM range, in vitro) decreased Abeta, Tau-hyperphosphorylation, GSK3beta activation, and prevented apoptosis and mitochondrial dysfunction via increased Bcl2/Bax. AF710B was a highly potent cognitive enhancer (rats: 1-30 and 10-100 mcg/kg, po in trihexyphenidyl- and MK801-induced passive avoidance impairments, respectively). AF710B had also 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, neuroinflammation, soluble and insoluble Abeta40, Abeta42, plaques and tau pathologies. AF710B differs from any sigma1, M1 muscarinic (allosteric, orthosteric or bi-topic) and sigma1/M1 agonists, respectively. AF710B induces a synchronized Sig1R activation and M1 muscarinic allosteric/bi-topic modulation via super-sensitization of M1mAChR, through a hypothetical heteromerization with Sig1R.

M1 muscarinic agonists can alter some pathologies in AD, Parkinson's disease and Lewy body dementia, yet AF710B has further benefits. In fact, AF710B is highly efficacious against major AD hallmarks (e.g. cognitive deficits, amyloid and tau pathologies, neuroinflammation, oxidative stress and mitochondrial dysfunctions). Thus AF710B has therapeutic advantages in AD and perhaps other protein-aggregation diseases vs. a plethora of experimental and licensed treatments.