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Designed multi target drugs initiating neuroprotection, neurorestoration and mitochondrial biogenesis via activation of PGC-1α for Alzheimer's disease

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Novel therapeutic approaches for the treatment of Alzheimer's disease (AD) comprise drug candidates designed specifically to act on multiple CNS targets, rather than a single receptor, as has been done with cholinesterase inhibitors. Major pathology of AD is the accumulation of iron in nucleus basalis, dentate gyrus, amyloid plaques and tangles and increase in monoamine oxidase (MAO). The iron contributes to the onset of oxidative stress and glutaminergic excitotoxicity via interaction with hydrogen peroxide generated by the reaction of MAO. We have synthesized several multi target non-toxic, brain permeable iron chelator drugs, such as M30, M30P and HLA20, possessing propargyl MAO and cholinesterase inhibitory moieties with neuroprotective and neurorestorative activities. These drugs possess anti-apoptotic, pro-survival neuro rescue effects, induction of neuronal differentiation, regulation of amyloid precursor protein (APP) and β-amyloid (Aβ) levels. They induce the outgrowth of neuritis in neuronal cell cultures, trigger cell cycle arrest in G0/G1 phase and enhance the expression of growth associated protein 43, HIF (hypoxia inducing factor) and increased brain levels of brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and erythropoietin. This has been shown to be associated with the inhibition of iron dependent prolyl-4-hydroxylase that regulates HIF. Both M30 and HLA20 process APP via activation of alpha secretase. They possess neurorestorative activity in in vivo models of Parkinson's disease and restore the cognitive deficit in APP/PSI double transgenic mice, the streptozotocin (STZ) Mc Gill rat transgenic models of AD. The dual control of mitochondrial biogenesis and energy metabolism is regulated by silent information regulator 1 and 3 (SIRT1 and SIRT3) and peroxisome proliferator activated receptor γ co-activator-1α (PGC-1α) is both activated by M300 and HLA20.