DISCOVERY OF A SERIES OF MOLECULES ACTING AS POTENT ALPHA7 NACHR AGONISTS WITH PRO-COGNITIVE AND NEUROPROTECTIVE PROPERTIES

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Nicotinic acetylcholine receptors of the alpha7 type have emerged as promising therapeutic targets for treatment of Alzheimer disease and schizophrenia owing to their involvement in cognition, memory and neurodegeneration. Using a functional FLIPR-based calcium assay employing the rat alpha7 nAChR stably expressed in a GH4C1 cell line, a novel chemical series of potent small molecule agonists of the alpha7 nAChR was discovered. Examples of this series were selective over alpha1, alpha4 nAChRs and 5HT-3 receptors and showed micromolar antagonistic activity at the alpha3 nAChR. Two prototypic compounds, SEN-WAY-1 and SEN-WAY-3, identified as partial and full agonist with an EC50 of 3.0 and 2.3 microM respectively are presented in greater detail. The neuroprotective potential of these compounds was investigated in an assay of NMDA-mediated neurotoxicity employing rat cortical neurons. Both SEN-WAY-1 and SEN-WAY-3 reduced significantly the NMDA induced toxicity. The pharmacological and neuroprotective properties of these small molecules were also investigated estensively *in vivo*. Following a single IP dose of 3 or 10 mg/kg, SEN-WAY-1 and SEN-WAY-3 were detected in the plasma and brain of rats resulting in brain-to-plasma ratios equal to or greater than 1 and Cmax concentrations above their FLIPR EC_{50} values. Effects on cognition were assessed in a model of short working memory (passive avoidance) and episodic memory (novel object recognition test). In both cognitive paradigms, SEN-WAY-1 and SEN-WAY-3 reversed the amnesic effects of scopolamine at a dose of 3 mg/kg when acutely administered (i.p.) after scopolamine injection. Neuroprotection was demonstrated in rats that had been lesioned by quisqualic acid injection in the nucleus basalis of Meynert (NBM). A sub-chronic treatment with 3 mg/kg SEN-WAY-1 or SEN-WAY-3 for 7 days significantly attenuated the decrease in the number of ChAT-positive neurons in this brain region. Therefore, like other known alpha 7 agonists, these new alpha7 nAChR agonists also demonstrate pro-cognitive and neuroprotective effects and may be useful for treating neurodegenerative diseases such as Alzheimer disease as well as neuropsychiatric disorders.