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In vitro pharmacological characterization and pro-cognitive effects of the selective alpha-7 nicotinic agonist WYE-103914

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Alpha-7 (α7) nicotinic acetylcholine receptor (nAChR) agonists are promising therapeutic candidates for the treatment of cognitive dysfunction associated with a variety of disorders including schizophrenia and Alzheimer's disease. We have identified WYE-103914 (SEN34625) as a novel α7 nAChR agonist with efficacy in preclinical rodent cognition models. WYE-103914 bound with high-affinity to the rat α7 nAChR expressed in GH4C1 cells with a Ki of 44 nM and increased intracellular Ca^{2+}, measured using FLIPR, with an EC_{50} of 130 nM (E_{max} 99%). WYE-103914 was >100-fold selective against the α1, α3, α4/β2 nAChRs receptors and the 5-HT_3-serotonin receptor subtype. Electrophysiological studies in α7 expressing GH4C1 cells confirmed the profile as an agonist with an EC_{50} of 490 nM and E_{max} of 70% at rat α7 expressed GH4C1 cells, and an EC_{50} value of 570 nM and E_{max} of 75% at human α7 receptor expressed in CHO cells. In vivo microdialysis studies revealed an increase in extracellular glutamate in the medial prefrontal cortex of freely moving rats at 10 mg/kg i.p.. In a rat novel object recognition (NOR) procedure (48-hr delay paradigm), WYE-103914 produced a statistically significant enhancement of visual learning and memory retention with an MED following oral dosing of 1 mg/kg, an effect blocked by pretreatment with the selective α7 receptor antagonist methyllycaconitine (5 mg/kg, i.p.). Utilizing a 1-hr delay NOR procedure the NMDA receptor antagonist MK-801, administered prior to the learning trial, produced a robust deficit in recognition memory. Pre-treatment with WYE-103914 reversed the memory disrupting effects of MK-801 (MED = 10 mg/kg, p.o.) in this model. Finally, WYE-103914 was also examined in a related model in mice using social odor recognition (SOR) as the paradigm. WYE-103914, treated concurrently with MK-801 immediately after training, produced a statistically significant reversal of MK-801 disrupted SOR at 3 mg/kg, p.o.. In addition, WYE-103914 administered immediately following training enhanced retention memory in SOR evaluated 6 days later (MED = 10 mg/kg, p.o.). Treatment with 3 mg/kg/day i.p. of WYE-103914 for 7 days also attenuated the decrease in the number of ChAT-positive neurons produced by the injection of quisqualic acid into the nucleus basalis magnocellularis. These data indicate that, similar to other α7 nAChR agonists, WYE-103914 exhibits a robust preclinical cognitive-enhancing and potential neuroprotective profile.

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Characterization of the alpha-7 nicotinic receptor agonist WYE-103914 in models relevant to schizophrenia and interaction with antipsychotics

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Alpha-7 (α7) nicotinic acetylcholine receptor (nAChR) agonists are promising therapeutic candidates for the treatment of cognitive disorders including schizophrenia and Alzheimer's disease. Given the intended clinical utility of α7 nAChR agonists, WYE-103914 (SEN34625), a novel α7 nAChR agonist with pro-cognitive activity in preclinical rodent models (see Dunlop et al., accompanying abstract), was evaluated in preclinical models relevant to schizophrenia alone and in the presence of antipsychotic drugs. The latter assessment is significantly lacking in terms of preclinical studies for such adjunct treatments for cognitive impairment in schizophrenia. In the rat pre-pulse inhibition (PPI) behavioral assay of pre-attentive processing and sensorimotor gating, WYE-103914, given acutely or chronically (14 day) reversed an MK-801 disruption of PPI (MED = 3 mg/kg, p.o.). WYE-103914 also improved sensory gating of the P50 auditory-evoked response (AER) in C57BL6J mice as evidenced by a decreased S2:S1 ratio in a paired AER paradigm (MED = 3 mg/kg, i.p.). In preclinical models predictive of antipsychotic efficacy, WYE-103914 (up to 54 mg/kg, i.p.) failed to block apomorphine-induced climbing (AIC) in mice, and failed to decrease conditioned avoidance responding in rats at doses up to 30 mg/kg, i.p.. The atypical antipsychotic risperidone significantly blocked climbing at lower doses than those required to impact apomorphine-induced stereotypy, and this profile of risperidone was not negatively affected by co-administration of WYE-103914 (10 mg/kg, p.o.). In conditioned avoidance responding model, risperidone (0.3 mg/kg, i.p.) produced a larger decrease in avoidance responding in the presence of WYE-103914 (3 mg/kg, p.o.) compared to risperidone alone. Finally, it was determined that the cognitive enhancing effect of WYE-103914 was preserved in the combined presence of risperidone. In the rat novel object recognition procedure, doses of risperidone in the range 0.03-3 mg/kg, i.p. produced a deficit in recognition memory when tested 1 hr after the initial learning trial. In the combined presence of an impairing dose of risperidone (0.03 mg/kg, i.p.), WYE-103914 (3 mg/kg, p.o.) maintained its procognitive efficacy. Taken together, these data validate the approach of adjunctive cognitive treatment with an α7 nAChR agonist and an antipsychotic drug, and that atypical antipsychotic drug activity is maintained in an adjunctive setting.

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