a7 Nicotinic Acetylcholine Receptor Agonists or Antagonists as Potential Cognition Enhancers?

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Introduction

• Activation of a7 nicotinic acetylcholine receptors (a7 nAChRs) through selective partial or full agonists and/or modulators, has been shown to improve cognitive function in both animal and human studies.

• Hence, a7 nAChRs may be attractive targets for cognition enhancement in for example Alzheimer’s disease (AD) and schizophrenia.

• The objective of the current study was to investigate the cognition enhancing properties of low dose administration of the selective a7 nAChR antagonist methyllycaconitine (MLA) in rats.

Results

Dose-response curve for a7 nAChR agonist EVP-6124

Procognitive effect induced by EVP-6124 reversed by selective a7 nAChR antagonist MLA (i.p.)

Procognitive effect induced by EVP-6124 reversed by selective a7 nAChR antagonist MLA (i.c.v.)

Conclusions

• The a7 nAChR agonist EVP-6124 showed procognitive effects in a natural forgetting paradigm of the ORT in rats. These effects were blocked by the selective a7 nAChR antagonist MLA, indicating that these procognitive effects were mediated through a7 nAChRs.

• Interestingly, low doses of MLA also significantly improved memory of rats in this ORT paradigm.

• Moreover, it was found that a dose of MLA that was too high (1.0 mg/kg, i.p.) to improve memory in the natural forgetting paradigm (24 h retention interval), was also sufficient to induce a memory deficit in a 1 h retention interval ORT.

• Among other possibilities, one explanation for these findings could be that a7 nAChR antagonists promote a7 nAChR resensitization.

• While the main focus of the a7 nAChR as a target for cognition enhancement lies on agonists and positive modulators, antagonists of these receptors might also prove to be a valuable tool for cognition enhancement in AD and/or schizophrenia.