α7 Nicotinic Acetylcholine Receptor Agonists or Antagonists as Potential Cognition Enhancers?

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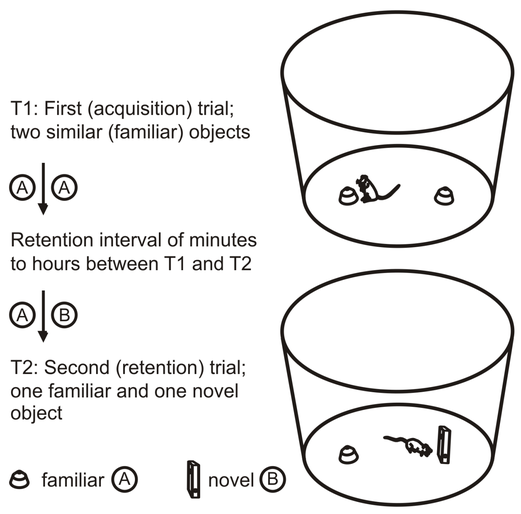
Introduction

• Activation of α7 nicotinic acetylcholine receptors (α7 nAChRs) through selective partial or full agonists and/or modulators, has been shown to improve cognitive function in both animal and human studies.

• Hence, α7 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 α7 nAChR antagonist methyllycaconitine (MLA) in rats.

Methods

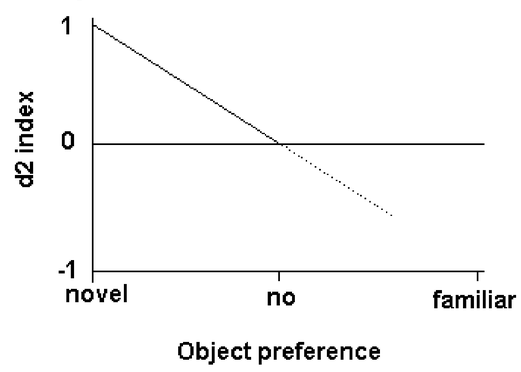


Schematic presentation of the test procedure of the Object Recognition Task (ORT)

Basic measures: time spent exploring the separate objects during T1 and T2

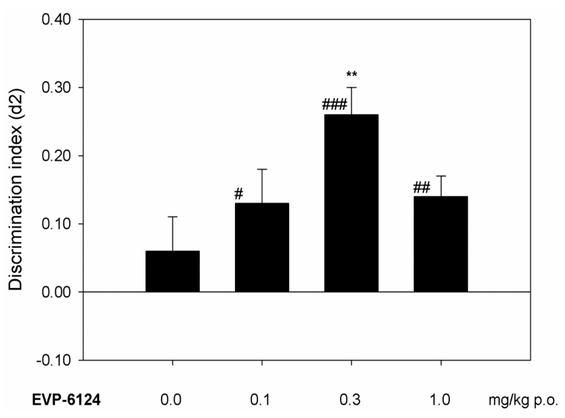
d2 index: relative measure of object discrimination during T2

• d2 = (b - a)/(a + b)
a=familiar object time, b=novel object time



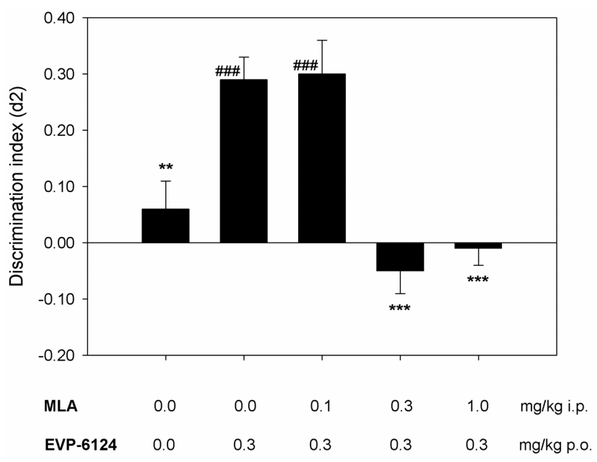
Results

Dose-response curve for α7 nAChR agonist EVP-6124



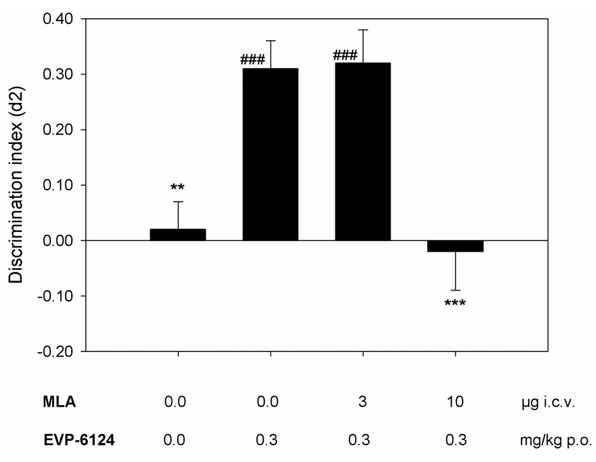
0.3 mg/kg EVP-6124 (p.o.) completely reversed the natural forgetting in the ORT. EVP-6124 was administered p.o. 30 min before T1.

Procognitive effect induced by EVP-6124 reversed by selective α7 nAChR antagonist MLA (i.p.)



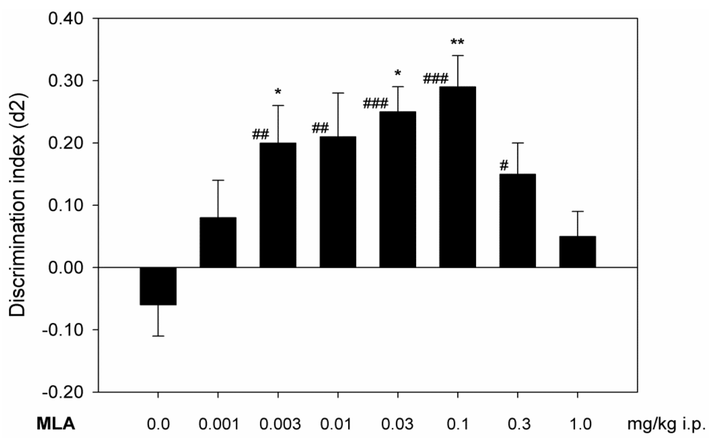
Peripheral administration of 0.3 mg/kg MLA (i.p.) completely reversed the procognitive effect of EVP-6124 in a natural forgetting paradigm of the ORT. EVP-6124 and MLA were administered 30 and 60 min before T1, respectively.

Procognitive effect induced by EVP-6124 reversed by selective α7 nAChR antagonist MLA (i.c.v.)



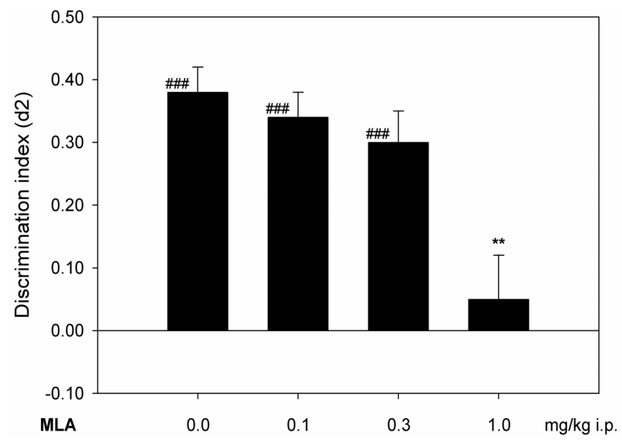
Central administration of 10 µg MLA (i.c.v.) completely reversed the procognitive effect of EVP-6124 in a natural forgetting paradigm of the ORT. EVP-6124 was administered p.o. 30 min before T1. MLA was adminstered 4 min before T1 (2 µl, 1µl/min).

Dose-response curve for α7 nAChR antagonist MLA



Peripheral administration of 0.003-0.1 mg/kg MLA (i.p.) showed procognitive effects in a natural forgetting paradigm of the ORT. MLA was administered 30 min before T1.

Inducing a memory deficit with MLA in a 1 h retention interval ORT



Peripheral administration of 1.0 mg/kg MLA (i.p.) induced a memory deficit in a 1-h retention interval ORT. MLA was administered 30 min before T1.

N=16-18 male Wistar rats per treatment

The T1-T2 retention interval was 24 h, except where otherwise indicated in the Figure header

*: one-way ANOVA/Repeated measures ANOVA → comparison with the vehicle condition (Post-hoc Bonferroni t-tests)

*P < 0.05; **P < 0.01; ***P < 0.001

#: one-sample t-tests → comparison with 0 (i.e. chance performance level)

#P < 0.05; ##P < 0.01; ###P < 0.001

Conclusions

•The α7 nAChR agonist EVP-6124 showed procognitive effects in a natural forgetting paradigm of the ORT in rats. These effects were blocked by the selective α7 nAChR antagonist MLA, indicating that these procognitive effects were mediated through α7 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 α7 nAChR antagonists promote α7 nAChR resensitization.

•While the main focus of the α7 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.

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