Methyllycocantine and scopolamine induced cognitive dysfunction: differential reversal effect of cognitive-enhancing drugs

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Introduction
It is now widely accepted that α7 nAChR plays a central role in cognitive deficits associated with neurodegenerative and cognitive disorders such as Alzheimer’s disease, Parkinson’s disease and schizophrenia. In support of this concept, changes in the brain expression of α7 nAChR have been reported in patients with neurodegenerative diseases. Furthermore, epidemiological studies have reported that nicotine decreases the risk for Parkinson’s and Alzheimer’s disease. Selective α7 nAChR agonists have been reported to improve the cognitive performance of rodents in various assays. Finally, the neuroprotective effect of galanthamine and donepezil has been demonstrated to be mediated by the stimulation of α7 nAChR in rat primary neurons.

To the best of our knowledge, there is not yet a well-established and specific in-vivo pharmacological model for studying cognitive deficit associated with the dysfunction of α7 nAChR.

Animal testing and measure of cognitive deficit
Male CD-1 mice are assessed for their spontaneous alternation in the T-maze. Spontaneous alternation is the innate tendency of rodents to alternate free choices in a T-maze over a series of successive runs. This sequential procedure relies on working memory and is sensitive to various pharmacological manipulations affecting memory processes.
The T-maze apparatus is made of gray Plexiglas with a main stem (55 cm long × 10 cm wide × 20 cm high) and two arms (30 cm long × 10 cm wide × 20 cm high) positioned at 90 degree angle relative to the main stem. A start box (15 cm long × 10 cm wide) is separated from the main stem by a guillotine door. Horizontal doors are also provided to close specific arms during the force choice alternation task.
The percentage of alternation over the 14 free-choice trials is determined for each mouse and is used as an index of working memory performance.

An alternation is defined as a succession of 2 different arms over consecutive choices (e.g., the sequence right-left-right represents 2 alternations).

Objectives
The aim of the present study is threefold:

- To assess whether specific inhibition of α7 nAChR induces cognitive deficit in mice; the effect of MLA, a reported specific antagonist of α7 nAChR, is investigated.
- To assess whether the cognitive deficit resulting from the inhibition of α7 nAChR could be reversed by clinically approved cognitive-enhancing drugs such as donepezil, memantine and galanthamine.
- To undertake a face to face comparison with traditional model involving muscarinic receptor antagonism, i.e., scopolamine-induced cognitive deficit

Summary of key findings

- Specific inhibition of α7 nAChR by MLA induces marked cognitive deficit in mice.
- MLA-induced cognitive deficit is comparable in intensity to that elicited by scopolamine (inhibition of muscarinic receptor).
- Donepezil and galanthamine show enhanced potency (1 to 3 logarithm magnitude, respectively) in MLA - as compared to scopolamine - induced cognitive deficit.
- Memantine reverses MLA-deficit whereas it is ineffective in scopolamine-deficit model.

Results
The degree of cognitive dysfunction is comparable in MLA and scopolamine-based assays but the MLA-deficit shows higher sensitivity and responsiveness to the current cognitive-enhancing drugs than scopolamine-deficit.

Figures

References