Reversal effect of donepezil on cognitive impairment induced by cholinergic and glutamatergic antagonists in mice

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Introduction

Cholinergic and glutamatergic systems have been implicated in cognitive dysfunction of psychiatric disorders such as Alzheimer's disease and schizophrenia. Muscarinic antagonism via systemic injection of scopolamine is used as a standard / reference drug for inducing cognitive deficits in healthy humans and animals. Other cholinergic and glutamatergic antagonists have been reported for their cognitive disrupting effect but they are also known to induce hypermobility. Therefore, their use as disruptor agent for an in-vivo model of cognitive impairment requires further validation.

Objective and approach

The goal of the present study is to characterize the cognitive deficit-induced by different cholinergic and glutamatergic antagonists in the mouse T-maze continuous alternation task. Special attention is addressed to the reversal effect of donepezil and the dissociation between cognitive impairment and hypermobility of mice.

Materials and Methods

Cognitive disruptor drugs :

- Scopolamine : antagonist of muscarinic receptors
- Methyllycaconitine (MLA) : specific antagonist of ∝7-nicotinic receptor
- MK-801 (dizocilpine) : antagonist of N-Methyl-D-aspartate (NMDA) receptor
- Phencyclidine (PCP) : antagonist of N-Methyl-D-aspartate (NMDA) receptor

Cognitive enhancing drug :

- Donepezil (Aricept ®): acetylcholinesterase inhibitor

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 sliding door. Horizontal doors are also provided to close specific arms during the force choice alternation task.

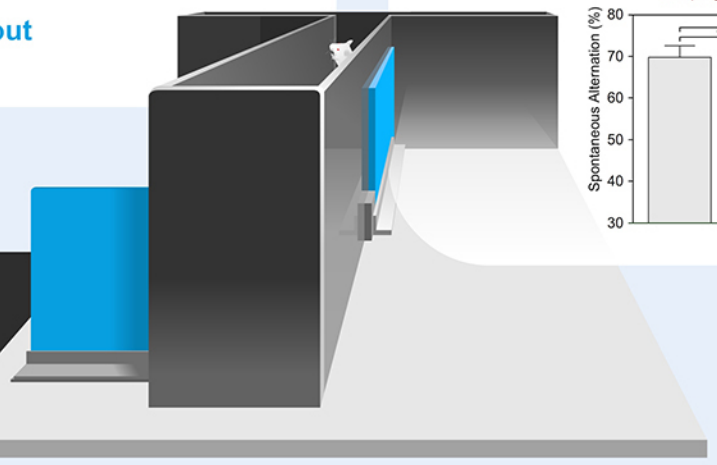
The percentage of alternation over the 14 free-choice trials is determined for each mouse and is used as an index of working memory performance. An alternation is defined as a succession of 2 different arms over consecutive choices (e.g., the sequence right-left-right represents 2 alternations).

Summary of key findings

- Inhibition of cholinergic or glutamatergic pathways results in cognitive dysfunction and hypermobility in mice
- Donepezil restores the cognitive function of mice without affecting their hypermobility

Conclusion

The cognitive dysfunction induced by cholinergic or glutamatergic antagonists is not a consequence of drug - induced hypermobility in the mouse T-maze task



Results

Scopolamine (muscarinic receptor antagonist) induces a significant reduction in the spontaneous alternation of mice in the T-maze and markedly reduces time to task completion, suggesting cognitive dysfunction and hypermobility. Similar pattern of results is reproduced when MLA (∝7-nicotinic receptor antagonist), MK-801 or PCP (NMDA receptor antagonists) is injected to mice.
Donepezil treatment reverses the drug-induced cognitive dysfunction without affecting the hypermobility of mice, regardless of the disruptor drug used.

Data are presented as mean ± sem of 10 animals. * , ** , *** denote statistical significance levels.

Figure 1 :

Effect of donepezil treatment on cognitive deficit and hypermobility behaviour of mice induced by scopolamine injection.
A : Spontaneous alternation of mice in the T-maze ; B : Time to completion of T-maze task

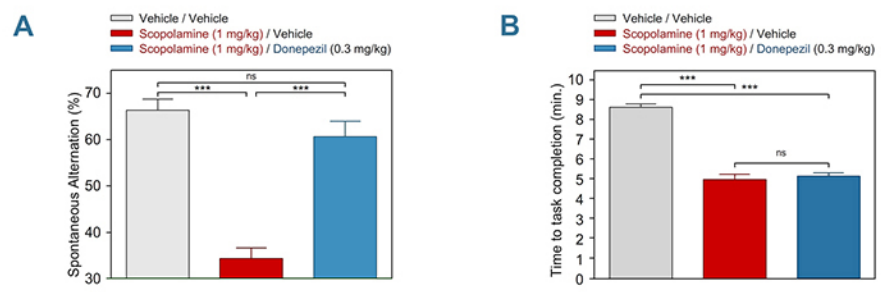


Figure 2 :

Effect of donepezil treatment on cognitive deficit and hypermobility behaviour of mice induced by MLA injection.
A : Spontaneous alternation of mice in the T-maze ; B : Time to completion of T-maze task

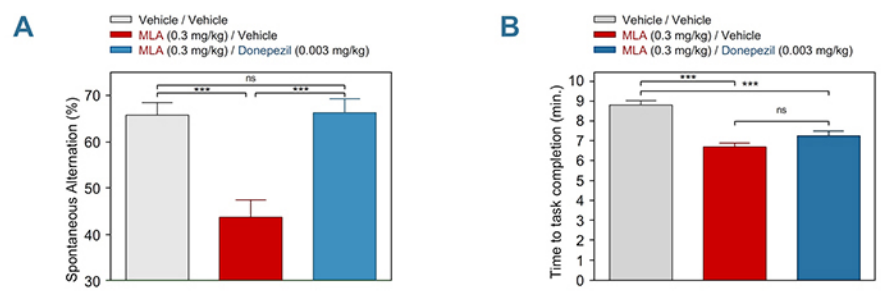


Figure 3 :

Effect of donepezil treatment on cognitive deficit and hypermobility behaviour of mice induced by MK-801 injection.
A : Spontaneous alternation of mice in the T-maze ; B : Time to completion of T-maze task.

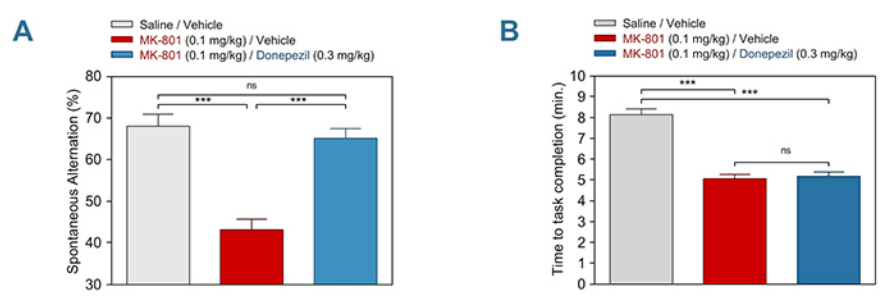


Figure 4 :

Effect of donepezil treatment on cognitive deficit and hypermobility behaviour of mice induced by PCP injection.
A : Spontaneous alternation of mice in the T-maze ; B : Time to completion of T-maze task.