Subchronic Donepezil prevents Amyloid-β-induced memory disruption in the rat

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Summary of key findings

- Donepezil shows neurotrophic effect on cortical neurons in cultures
- Acute and subchronic Donepezil significantly reverse scopolamine-induced memory deficit in rats
- Subchronic but not acute Donepezil significantly improves the acquisition of dark avoidance in amyloid-β rats
- Subchronic but not acute Donepezil was associated with improved retention of dark avoidance information in amyloid-β rats

Introduction

Alzheimer's disease (AD) is neurodegenerative disorder that impairs the cognitive function. While there is no cure for AD, Cholinestrease inhibitors are approved to treat its main cognitive symptoms (memory deficit). Donepezil (Aricept®) is the most prescribed therapy for AD.
Besides its symptomatic action, recent clinical study shows evidence of lower rate of hippocampal atrophy in Alzheimer's disease patients treated with Donepezil.
This is in line with numerous preclinical results showing neuroprotective effect of Donepezil.

Materials and Methods

Scopolamine-induced memory deficit

Naïve male rats are injected, i.p., with 0.6 mg/kg of scopolamine immediately after the acquisition of dark avoidance. Animals are assessed for their memory performance in the passive avoidance test 24h after scopolamine injection.

Model of i.c.v. Amyloid-β injection

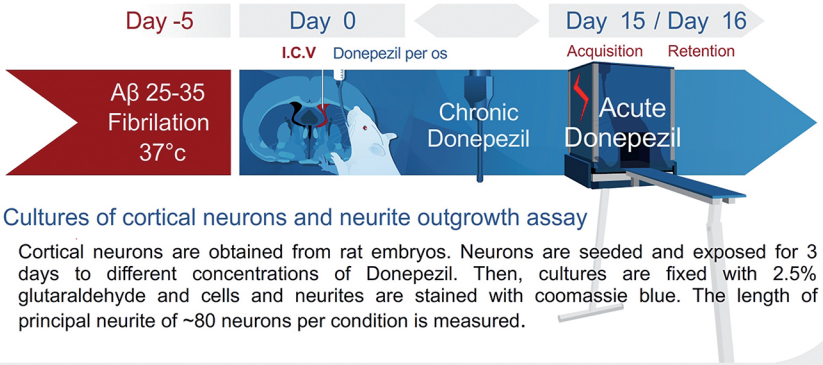
Male Wistar rats are injected, i.c.v., with fibrillated amyloid-β. Animals are assessed for their learning memory performance in the passive avoidance test 2 weeks after the i.c.v. injection.

Passive avoidance test

The test comprises 2 sessions: acquisition and retention.

- In the acquisition, the rat is placed in the extremity of the illuminated runway. Once the rat has entered into the dark compartment, the door is closed and a foot shock is administered. This trial is repeated (max 10 trials) until the latency to enter the dark compartment (STL, Step-Through-Latency) is greater than 120 s. The number of trials until acquisition of dark avoidance is recorded.
- One trial retention session is performed 24 h later. STL is recorded during the retention trial.

Diagram of experimental design and Donepezil treatment



Cultures of cortical neurons and neurite outgrowth assay

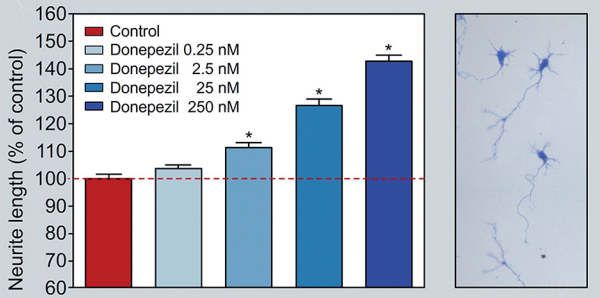
Cortical neurons are obtained from rat embryos. Neurons are seeded and exposed for 3 days to different concentrations of Donepezil. Then, cultures are fixed with 2.5% glutaraldehyde and cells and neurites are stained with coomassie blue. The length of principal neurite of ~80 neurons per condition is measured.

Objectives

The aims of the present study are:

- to assess whether treatment with Donepezil improves learning / memory deficit in a rat model of AD induced by intracerebroventricular (i.c.v) administration of fibrillated amyloid-β (β 25-35) peptide.
- to assess whether or not Donepezil acts through its cognitive enhancing effect
- assess whether or not Donepezil exposure could induce modifications in primary cortical neurons in cultures.

Figure 1 — **Neurotrophic effect of Donepezil on cortical neurons**



Three days exposure of Donepezil to cortical neurons in culture enhances neurite outgrowth in dose-dependent manner.

Figure 2 — **Cognitive enhancing effect of Donepezil**

Injection of scopolamine after the acquisition of dark avoidance elicits a dramatic decrease in the STL, suggesting a memory deficit.

- Subchronic and acute Donepezil produce an increase in STL of scopolamine rats, suggesting cognitive enhancing action of Donepezil.
- Subchronic and acute Donepezil show comparable degree of cognitive recovery in scopolamine rats.

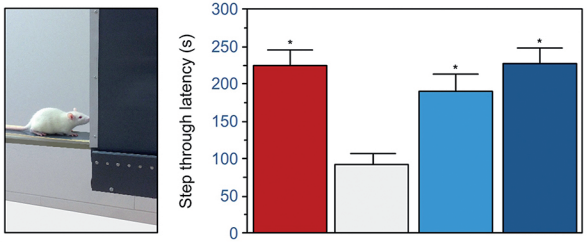
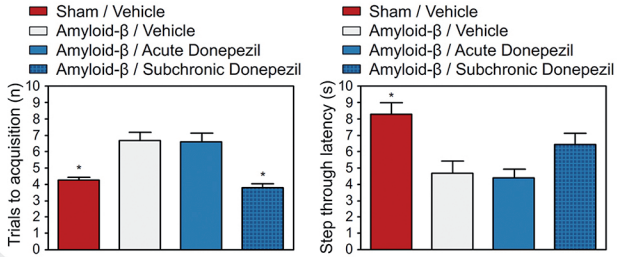


Figure 3 — **Improved learning / memory in Aβ rats treated with subchronic Donepezil**

Within 2 weeks, Aβ injection induces significant increase in number of trials to acquire dark avoidance and reduces the STL, suggesting learning / memory deficit.

Whilst subchronic Donepezil reverts the performance of Aβ rats to the level of Sham specimen, acute Donepezil does not produce any change. This suggests that the beneficial effect of subchronic Donepezil on learning / memory dysfunction of Aβ rats cannot be recapitulated by acute Donepezil treatment.



Conclusion

Subchronic donepezil prevents amyloid-β-induced memory disruption in the rat. This beneficial effect of Donepezil is not a result of its pro-cognitive action