Animal model of cognitive dysfunction responding to ADHD therapies

NEUROFIT PRECLINICAL RESEARCH

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Introduction

Over 90% of adults and children living with and seeking treatment for **Attention Deficit Hyperactivity Disorder** (ADHD) manifest cognitive dysfunction, particularly impairments in attention, working memory and executive function which provides support for a cognitive rather than psychomotor basis of ADHD pathology.
The existing animal models for ADHD feature psychomotor behavior impairments (impulsivity and hyperactivity) but do not always favorably respond to the psychostimulant drugs used for the treatment of ADHD.

Objectives

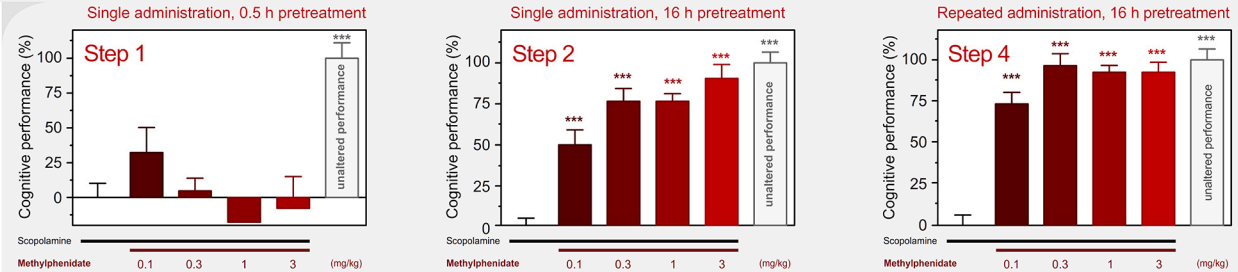
To study the potential of ADHD medications (methylphenidate, amphetamine and atomoxetine) to restore the cognitive performance (spontaneous and continuous alternation in the T-maze) in mice with impaired cholinergic system via administration of scopolamine. The impact of treatment duration (single or repeated) as well as the pretreatment time before the T-maze test (short or longer) is studied.

Experimental design

Subjects: Male CD-1 mice (25-35 g) receiving 1 mg/kg scopolamine 0.5 h before the assessment of cognitive function in the T-maze.
The experimental plan follows a stepwise approach, i.e., the protocol implemented for the next experiment depends on the outcome of the preceding one.

	Methyphenidate	Amphetamine	Atomoxetine
Step 1 Single administration Short pretreatment interval (0.5 h before T-maze)	0.1 - 0.3 - 1 - 3 mg / kg	0.01 - 0.1 - 0.3 mg / kg	0.3 - 1 - 3 mg/kg
Step 2 Single administration Long pretreatment interval (16 h before T-maze)	0.1 - 0.3 - 1 - 3 mg / kg	0.01 - 0.1 - 0.3 - 1 mg / kg	
Step 3 Repeated administration (3 days) Short pretreatment interval (0.5 h before T-maze)			0.3 - 1 - 10 mg/kg
Step 4 Repeated administration (3 days) Long pretreatment interval (16 h before T-maze)	0.1 - 0.3 - 1 - 3 mg / kg	0.01 - 0.1 - 0.3 mg / kg	

Figure 1: Methylphenidate (dopamine transporter inhibitor)

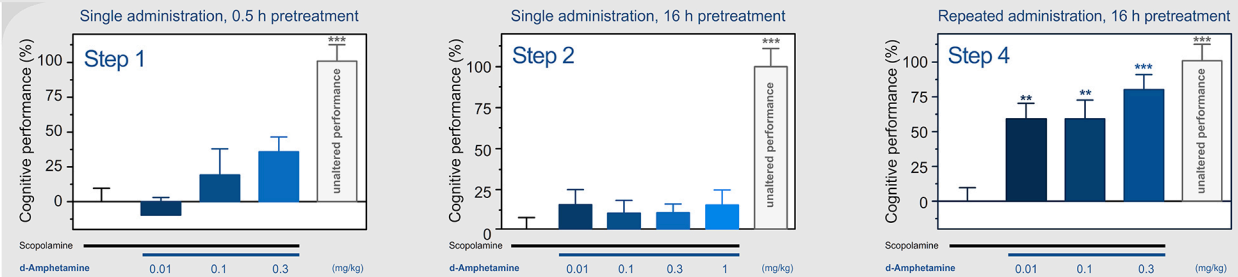


Single administration of Methylphenidate with short pretreatment time (0.5 h) does not improve the cognitive deficit observed in scopolamine-treated mice.

Single administration of Methylphenidate but with longer pretreatment time (16 h) restores the cognitive performance of scopolamine-treated mice.

3 days repeated administration of Methylphenidate with longer pretreatment time (16 h) fully restores the cognitive performance of scopolamine-treated mice.

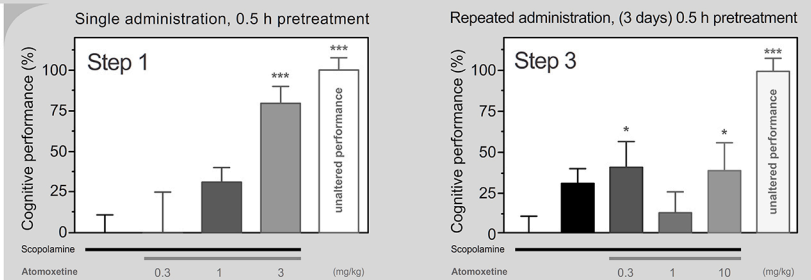
Figure 2: Amphetamine (monoamine releasing agent)



Single administration of Amphetamine does not improve the cognitive deficit observed in scopolamine treated mice regardless of the duration of the pretreatment time.

7 days repeated administration of Methylphenidate with longer pretreatment time (16 h) markedly improves the cognitive performance of scopolamine treated mice.

Figure 3: Atomoxetine (norepinephrine transporter inhibitor)



Single administration of Atomoxetine restores the cognitive performance of scopolamine-treated mice.

3 days repeated administration of Atomoxetine significantly improves the cognitive performance of scopolamine-treated mice.

Single administration of Atomoxetine is more effective in restoring the cognitive function of mice than repeated administration regimen

Key points

- Cognitive enhancing effect of ADHD medication can be evidenced in a mouse model of cognitive deficit caused by impairment of the cholinergic system.
- The pretreatment time as well as the treatment regimen influence the appearance cognitive enhancing effect of ADHD drugs. Whilst the treatment regimen is assumed to affect the exposure, the pretreatment time potentially conditions the presence or not of side effect (confounding factor) at the time of cognitive assessment.