

ACD856, A POSITIVE MODULATOR OF NEUROTROPHIN SIGNALING REVERSES SCOPOLAMINE- OR AGE-INDUCED COGNITIVE DEFICITS

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Introduction

The neurotrophins nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) regulate neuronal functions such as survival, differentiation and plasticity. Decreased NGF-signalling contributes to the dysfunction of basal forebrain cholinergic neurons during the course of Alzheimer's disease (AD) whereas increased BDNF signalling has been demonstrated to mediate improved synaptic plasticity during different pathological conditions. Interestingly, the Val66Met-BDNF polymorphism has been demonstrated to affect the anatomy of hippocampus and prefrontal cortex in normal individuals and to modulate episodic memory, hippocampal function and hippocampal volume in patients with either sporadic or familial Alzheimer's disease. The strong genetic linkage between dysfunctional BDNF signaling and familial and sporadic AD and the central involvement of NGF in cholinergic function strongly support and validate the development of stimulators of NGF and BDNF signaling as cognitive enhancers for AD.

Methods

ACD856 was characterized in several *in vitro* and *ex vivo* functional assays including TrkA or TrkB expressing cells and mouse primary cortical. The effects of ACD856 was also investigated in different *in vivo* behavioural models, i.e. scopolamine-induced memory impairment and in old animals with a reduced cognitive capability in the passive avoidance model, forced swim test and in Y-maze. Moreover, the effect of sub cutaneous administration of ACD856 on neurotransmitter release in the ventral hippocampus was investigated by microdialysis in freely moving rats.

Results

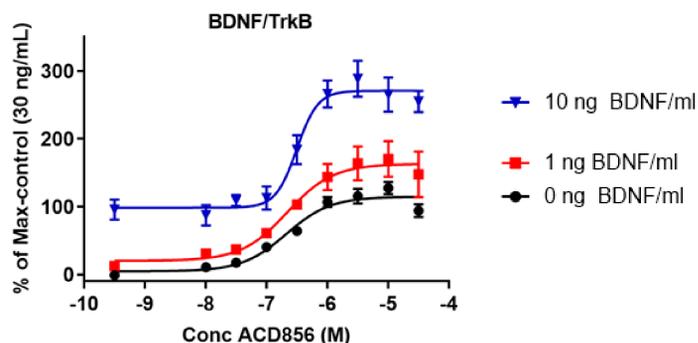
ACD856 enhance BDNF/TrkB signalling in a cell-based assays with modulatory as well as agonistic properties (fig 1). ACD856 potentiate BDNF signalling and phosphorylation of ERK1/2 in primary cortical neurons (data not shown). Subcutaneous administration of ACD856 results in increased levels of the neurotransmitters serotonin (5-hydroxytryptamine (5-HT)), noradrenalin (NA) and dopamine (DA) in the ventral part of hippocampus as measured by microdialysis. There was a significant increase in the amount of serotonin released after administration of ACD856 as compared to vehicle and a clear trend of increased levels of both noradrenalin and dopamine (fig. 2).

In vivo experiments demonstrate that ACD856 significantly and almost fully reverse scopolamine-induced memory impairments in mice in the passive avoidance (PA) model (fig 3). There was a statistically significant improvement of memory performance when administering ACD856 either pre-training, post-training or even pre-test. Administration of ACD856 at these three different timepoints is likely to address three different parts of memory, i.e. acquisition, consolidation or retrieval of a memory.

Interestingly, ACD856 was able to improve long-term memory in old animals (20 months of age). As can be seen in figure 4, there was a trend to improved memory already 24 hours after administration of ACD856 and the training session. The improvement of memory in naïve old animals was statistically significant after the second measurement, which occurred 11 days after administration of ACD856.

The clinical candidate and predecessor to ACD856, i.e. ACD855, was investigated as a cognitive enhancer in clinical phase 1 studies. Due to unexpected long half-life in man, ACD855 was discontinued as a cognitive enhancer. ACD856 is currently in clinical trials to evaluate its pharmacokinetic properties in man. A comparison of the pharmacokinetic profiles of ACD855 and ACD856 after oral administration in rats is demonstrated in figure 5.

Figure 1. Dose-response effects of ACD856 on TrkB-signaling at different concentrations of BDNF



Conclusion

We have demonstrated that ACD856 act as an enhancer of BDNF/TrkB signaling, increases neurotransmitter release in the hippocampus and act as a cognitive enhancer, thus suggesting its use for the treatment of cognitive dysfunction in AD. Interestingly, ACD856 improves long-term memory in naïve old animals and has promising pharmacodynamic and pharmacokinetic properties and is currently in clinical trials in man.

Figure 2. Effects of ACD856 on release of neurotransmitters in ventral hippocampus

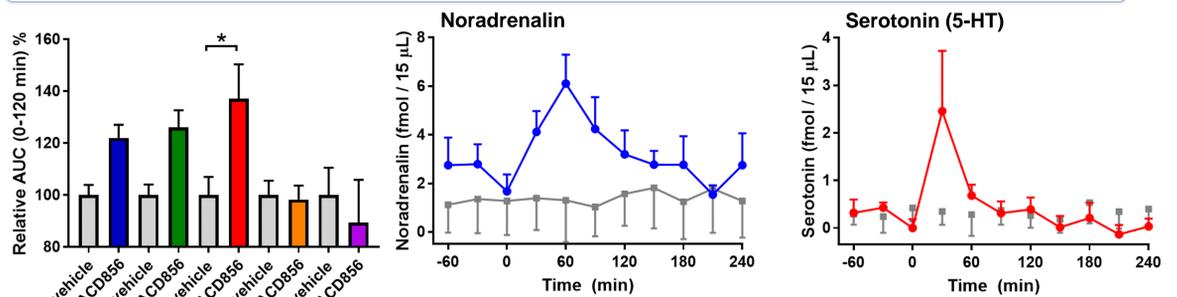


Figure 3. Effects of ACD856 on different memory paradigms in the passive avoidance model

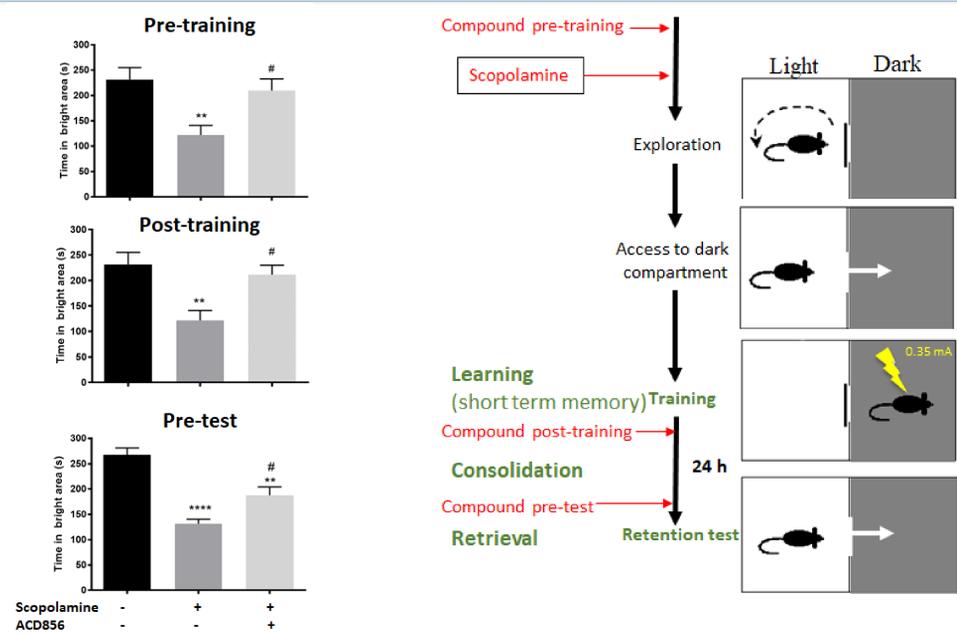


Figure 4. Effects of ACD856 on long-term or working memory in old mice

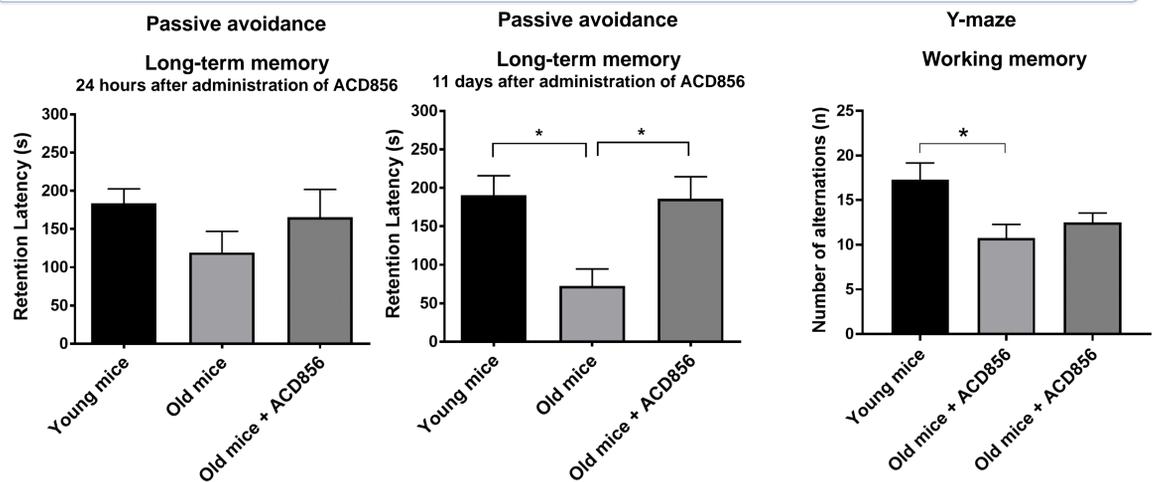


Figure 5. Pharmacokinetic profile of ACD855 or ACD856 in rats after oral administration

