IDENTIFICATION OF A POSITIVE MODULATOR OF NEUROTROPHIN RECEPTORS WITH POSITIVE EFFECT ON MITOCHONDRIAL FUNCTION AND MEMORY-ENHANCING EFFECTS

Cristina Parrado-Fernández, PhD, Gunnar Nordvall PhD, Nather Madjid PhD, Maria Backlund PhD, Magnus Halldin PhD, Johan Sandin PhD and Pontus Forsell PhD

AlzeCure

Aims

BDNF and NGF are key neurotrophins expressed in the brain and peripheral tissues that regulate many aspects of neuronal function such as proliferation, synaptic plasticity, and mitochondrial biogenesis, which all play a crucial role at the functional level e.g. mediating cognitive abilities. Furthermore, effects of the BDNF-Val66Met polymorphism points to BDNF as being of importance for the pathophysiology of cognitive impairment in patients with AD or PD. The aim of this study was to investigate the effects of a positive modulator of neurotrophin receptors on cognition and mitochondrial function.

Methods

Positive modulators of BDNF and NGF signaling were identified by an HTS and characterized using cell-based assays to study for BDNF- or NGF-induced activation of the receptors and the concomitant association of SHC1 to the TrkA- and TrkB-receptors. Effects of AC-0027136 were investigated in vivo using scopolamine-induced or age-related memory impairment in a fear conditioning paradigm, the Passive Avoidance test. Effects of AC-0027136 on mitochondrial function was investigated in primary mouse cortical neurons by measuring metabolic activity and ATP production.

Results

AC-0027136 was identified as a positive modulator of NGF/TrkA and BDNF/TrkB signaling (**fig 1**). In vivo models showed that AC-0027136 can attenuate scopolamine-induced memory impairment in mice and significantly improve long-term memory in aged animals (**figs 2 and 3**). Secondary tests in primary mouse cortical neurons demonstrate a dose-dependent positive effect of both neurotrophins and AC-0027136 on metabolic activity and mitochondrial ATP production relative to vehicle-treated control (**figs 4 and 5**).

In vitro pharmacology

AC-0027136 is a positive modulator of neurotrophin signaling

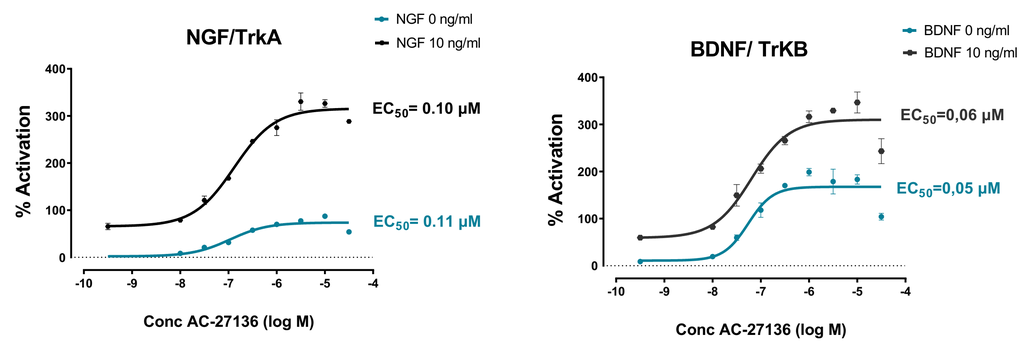

Figure 1. Effects of AC-0027136 on TrkA or TrkB signaling

AC-0027136 acts as a potent enhancer of human neurotrophin signaling with EC_{50} values of 100 nM and 50 nM, respectively for TrkA and TrkB receptors, and it shows agonistic properties in cell-based assays.

In vivo efficacy

Memory-enhancing effects of AC-0027136 on different memory paradigms in the Passive Avoidance test

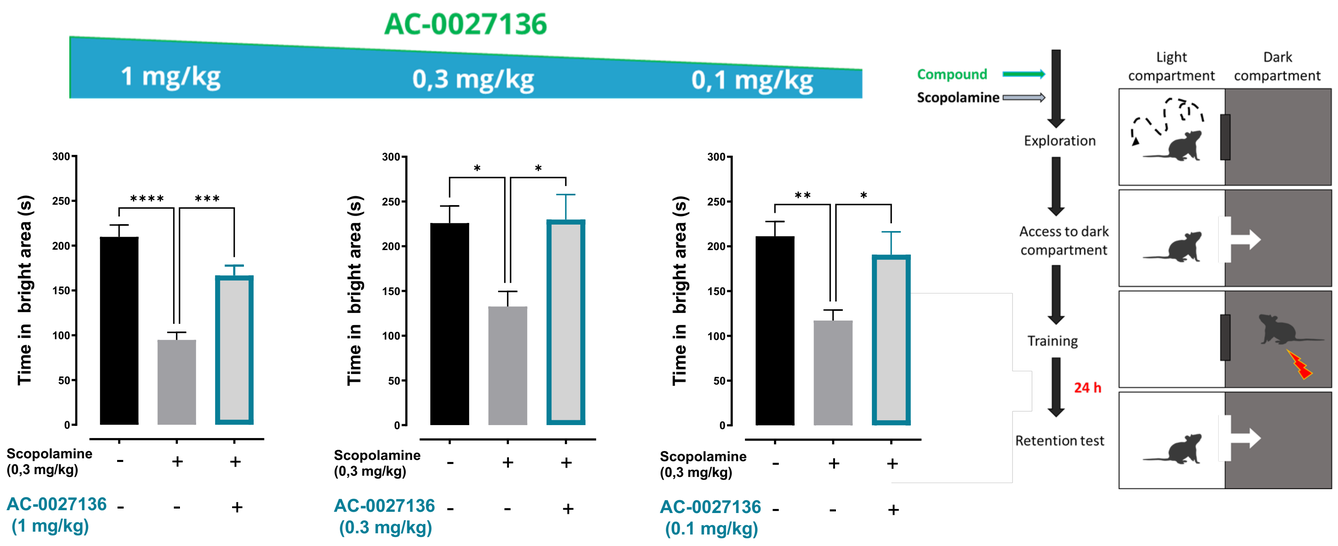

Figure 2. Effects of AC-0027136 on scopolamine–induced memory impairment test

AC-0027136 reverses scopolamine induced memory impairment with significant effect at the lowest single dose of 0,1 mg/kg

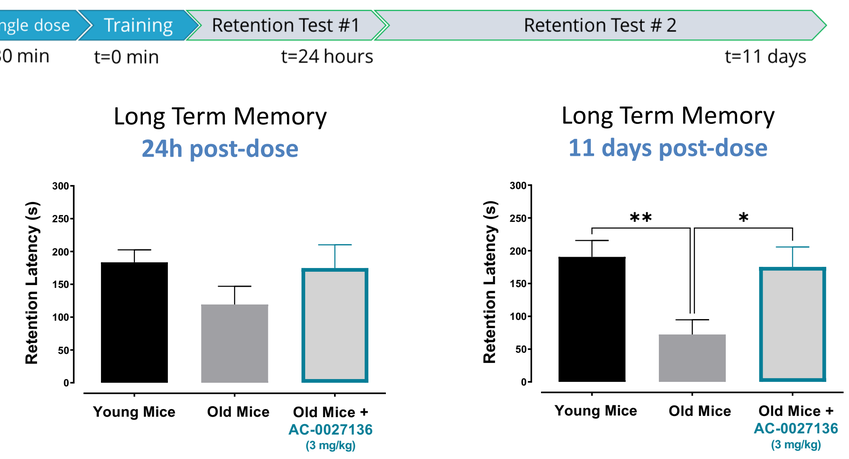

Figure 3. Effects of 3 mg/kg AC-0027136 on long-term memory

AC-0027136 reverses age-induced cognitive impairment in old-mice tested 11 day after dosing to a level similar to young mice

Primary Mouse Cortical Neurons: Positive effects of AC-0027136 on mitochondrial function

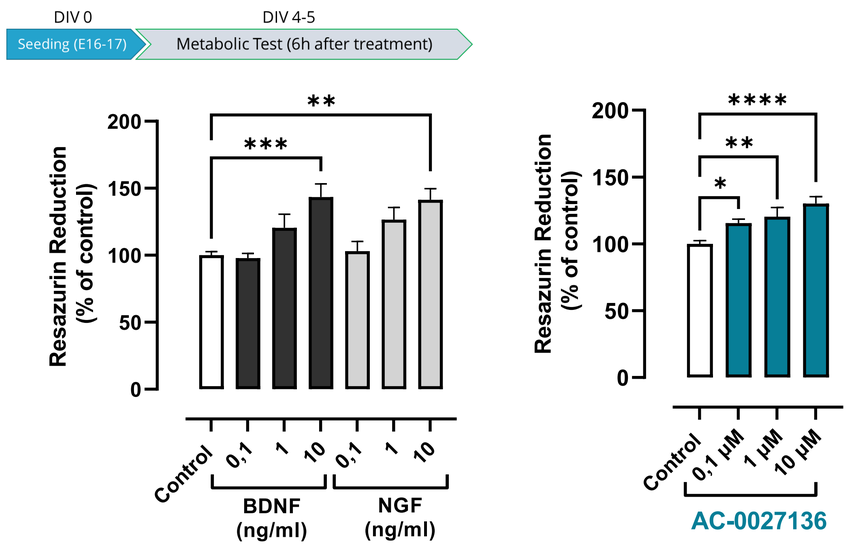

Figure 4. Effects of BDNF, NGF and AC-0027136 on metabolic activity in cortical neurons at DIV4-5 (n=3).

AC-0027136 increases metabolic activity in a dose-response manner in a cell media containing glutamine as the main energy source (No glucose, no pyruvate)

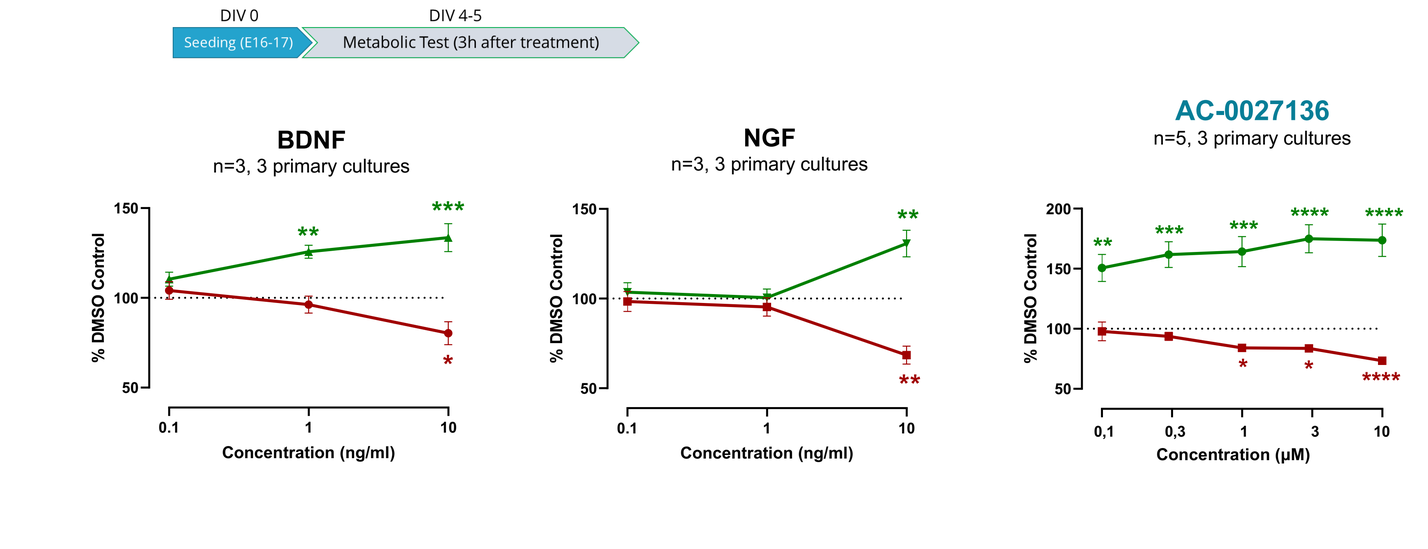

Figure 4. Effects of BDNF, NGF and AC-0027136 on ATP levels and Cytotoxicity in cortical neurons at DIV4-5 (n=3).

BDNF and NGF significantly increase ATP levels above concentrations of 1 and 10 ng/ml followed by a significant decrease in cytotoxicity at 10 ng/ml. AC-0027136 enhances ATP levels above 0,1 uM and shows decreased cytotoxicity above 1 uM.

Conclusions

We have identified AC-0027136 as a positive modulator of neurotrophin receptors with beneficial effects on cognition and with promising properties as a mitochondrial enhancer in neurons. Our findings demonstrate that AC-0027136 act as a cognitive enhancer and improves mitochondrial function, which could be of importance for the treatment of neurodegenerative diseases characterized by reduced cognition and mitochondrial function.

Alzecure Pharma AB
Hälsovägen 7
141 57 Huddinge
Sweden

AlzeCure

E-mail: cristina.parrado@alzecurepharma.com
Phone: +46 (0)735 332142
www.alzecurepharma.se

For further information please contact:
Martin Jönsson, CEO Tel: +46 707 86 94 43
martin.jonsson@alzecurepharma.com