Development of novel γ-secretase modulators for the treatment of Alzheimer's disease

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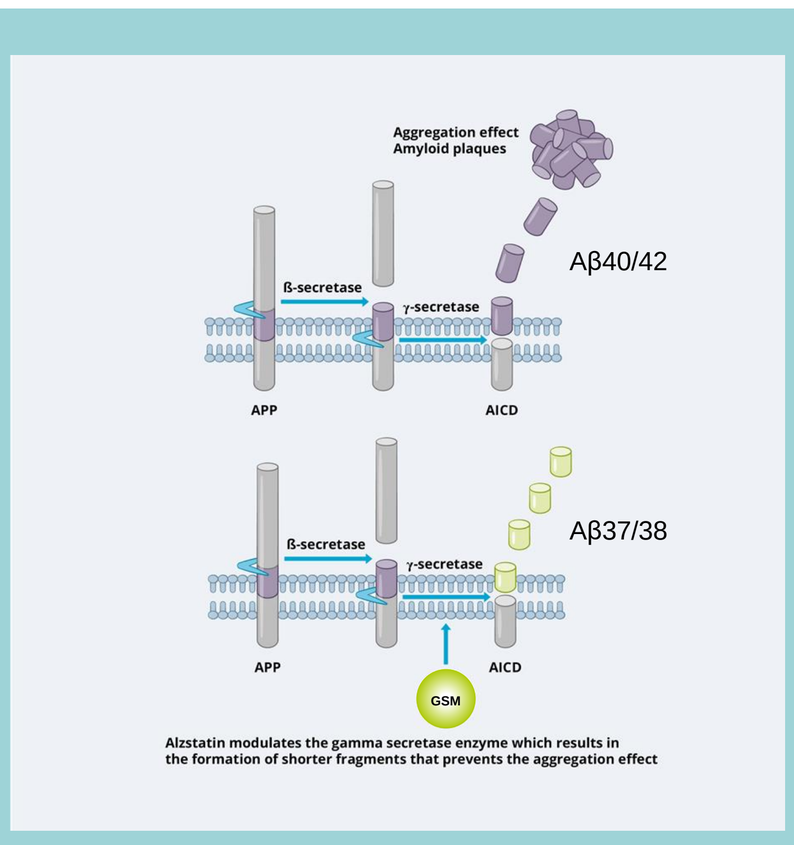

Conclusion

γ-secretase modulators (GSMs), as developed within the Alzstatin platform, are a novel class of compounds that alters the cleavage of amyloid precursor protein (APP) to less amyloidogenic peptides. Our data show that AC-0027875 reduces Aβ42, with a rapid onset and a long-lasting effect, in line with high brain tissue exposure. Further analysis will be needed to characterize the pharmacokinetics, the pharmacodynamic effects and the safety profile. In summary, our data suggest that GSMs such as AC-0027875 are a highly promising anti-amyloidogenic therapy for the treatment of early Alzheimer's disease (AD).

Introduction

Aggregation of the Aβ42 peptide results in amyloid plaque formation, a process that plays a pivotal role in early Alzheimer's disease (AD) pathogenesis. To interfere with Aβ42 production and amyloid plaque formation is therefore a prioritized therapeutic strategy.

γ-Secretase modulators (GSMs) represent a promising class of Aβ42-lowering anti-amyloidogenic compounds for the treatment of AD. GSMs exhibit several key features that make them suitable for the treatment of pre-symptomatic AD: 1) they reduce amyloidogenic Aβ42 production, while stimulating the formation of the shorter, less amyloidogenic peptides Aβ37 and Aβ38, and 2) they modulate without affecting the total γ-secretase activity, thus sparing the γ-secretase-mediated processing of other substrates, such as Notch, a property that is of central importance from a safety perspective.

Thus, treatment with GSMs decrease the level of Aβ42 and increase the level of Aβ38. High levels of the shorter Aβ38 has indeed been shown to reduce the cognitive decline and to reduce the risk for conversion to AD dementia (Cullen, Neurology, ahead of print Dec 2021).

Objectives

In this work, we set out to explore the *in vitro* and *in vivo* effect of AC-0027875, a novel potent GSM, on brain Aβ42 reduction in cells and animals as well as to assess its pharmacokinetic properties.

Methods

The effect of AC-0027875 on Aβ42 production was explored in HEK/APPswe cells and mouse primary cortical neurons (DIV 5) and analyzed with an Aβ42 specific ELISA.

A single oral dose AC-0027875 (60 µmol/kg) was administered to C57BL/6J mice and plasma and brain were collected at 15 min (only plasma), 30 min, 1 hr, 3 hr and 6 hr. The exposure in plasma and brain tissue was determined as well as the reduction of soluble Aβ42 in the brain.

Results

AC-0027875 efficiently reduced Aβ42 production in HEK/APPswe cells and in mouse primary cortical neurons (mPCN) with an IC_{50} of 7 nM (±1.4, n=3) and 5 nM (n=1), respectively.

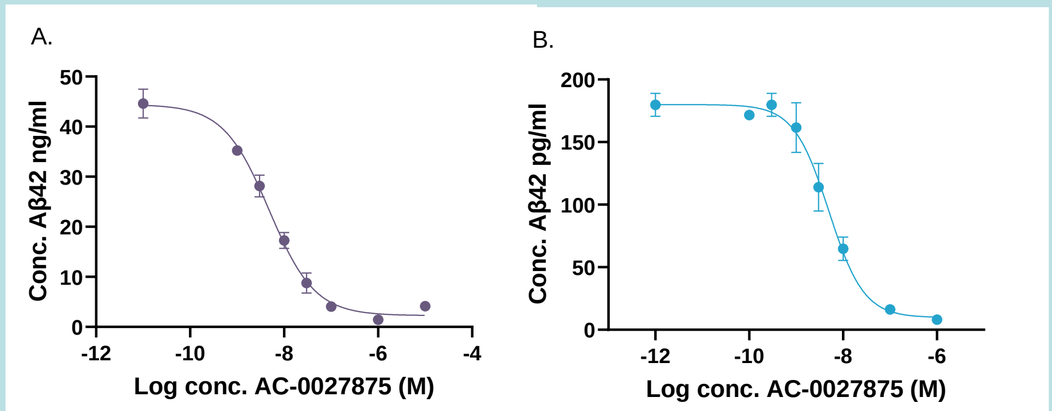

Figure 1. HEK APP/swe cells (A.) and mPCN (B.) were treated with different concentrations of AC-0027875. The amount of Aβ42 formed were analyzed using ELISA.

The novel potent GSM AC-0027875 has high mouse plasma and brain tissue exposure after oral administration with the free plasma and brain tissue exposure well above the IC50´s obtained in HEK/APPswe cells or in PCN:s. Furthermore, AC-0027875 efficiently lowered Aβ42 in the brain in a time-dependent manner.

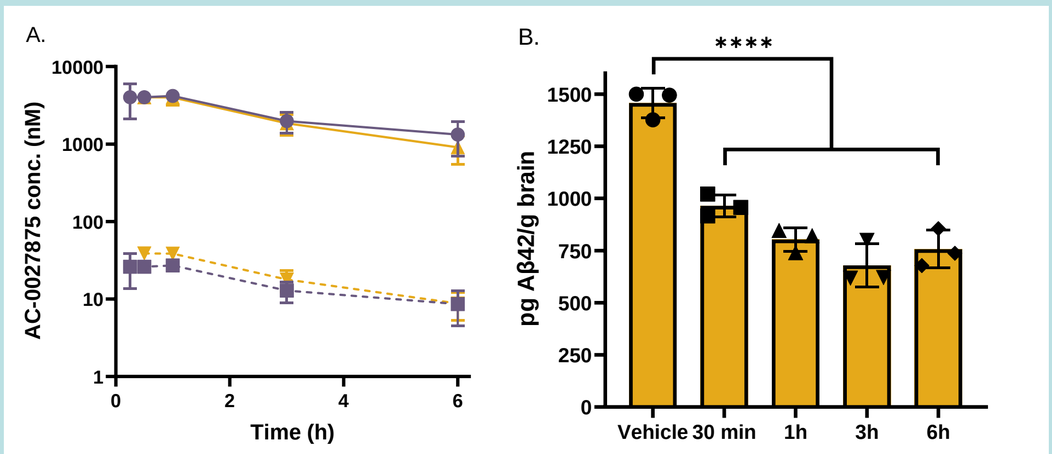

Figure 2. C57BL/6J mice were treated with a single oral dose of 60 µmol/kg AC-0027875 and plasma and brain were collected. In (A.) the PK profile of AC-0027875 is shown (Mean±SD). Solid and dotted lines are total and free concentration in plasma (purple) and brain tissue (orange), respectively. In (B) brain tissue levels of Aβ42 is shown. The amount of Aβ42 is significantly reduced in all treatment groups as compared to vehicle group (Mean±SD, One-way ANOVA with Dunnett's multiple comparisons test, ****p < 0.0001).

AC-0027875 has a promising profile as a potential anti-amyloidogenic therapy. Additional studies to fully characterize AC-0027875 in vivo are in progress.

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