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

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Objectives

Gamma-secretase modulators (GSMs) represent a promising class of Aβ42-lowering anti-amyloidogenic compounds for the treatment of Alzheimer's disease (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 gamma-secretase activity, a property that is of central importance from a safety perspective. As such, GSMs modulate the formation of secreted Aβ, while sparing the gamma-secretase-mediated processing of other substrates, such as Notch. High levels of the shorter Aβ38, which is increased after treatment with a GSM, has indeed been shown to reduce the cognitive decline and to reduce the risk for conversion to AD dementia (Cullen, 2022).

In this work, we set out to explore the in vitro and 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 (mPCN) (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, 1hr, 3hr and 6hr. 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 primary cortical neurons with an IC50 of 7 nM and 5 nM, respectively. Furthermore, we demonstrate that 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 $IC_{50's}$ obtained in HEK/APPswe cells or in cortical neurons. Furthermore, AC-0027875 efficiently lowered Aβ42 in the brain in a time-dependent manner. The animals displayed no acute clinical symptoms or abnormal behavior after a single dose of AC-0027875, despite the fact that high levels of the compound were reached in plasma and brain.

Conclusion

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.