AMELIORATION OF COGNITIVE DEFICITS IN APP TRANSGENIC MICE WITH SUBCHRONIC TREATMENT OF A γ-SECRETASE MODULATOR BUT NOT INHIBITORS

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Introduction: Elevation of brain amyloid-β(Aβ) peptides, particularly Aβ42, is thought to be a main cause of Alzheimer’s disease (AD). Gamma-secretase inhibitors (GSIs) can efficiently reduce Aβ levels but inevitably increase the substrate β-carboxyl-terminal fragment of amyloid precursor protein (APP-β-CTF), which may have deteriorating effects on synapses. We examined the effects of GSIs on cognition in both AD-model mice and normal mice in comparison with a γ-secretase modulator (GSM), which can lower Aβ42 levels without increasing β-CTF.

Aims: To elucidate differences between GSIs and GSMS in the effects on the cognition

Methods: A GSM (WO2007125364) or two GSIs (LY450139 or BMS-708163) were orally administered to five-month-old APP-Swedish mutant transgenic mice (Tg2576) or wild-type mice. Y-maze tests were conducted to evaluate working memory, and hippocampal levels of Aβ42, Aβ40, and β-CTF were measured via ELISA.

Results: Acute dosing with both the GSM and GSIs significantly ameliorated the cognitive deficits in Tg2576 mice. In contrast, subchronic treatment for eight days with the GSIs failed to improve the deficits, although subchronic treatment with the GSM still significantly improved them. Further, subchronic treatment with the GSI, but not the GSM, significantly impaired the working memory in wild-type mice. The maximum reductions of brain Aβ42 in Tg2576 were similar for all three groups, but increases in β-CTF were observed only in the GSI-treated groups.

Conclusions: Subchronic treatment with GSIs negatively affected cognition in mice, which was not the case with a GSM. Potential links between the increase in β-CTF and cognitive dysfunction remain to be elucidated.