Cathepsin B Knockout Reduces pGlu-Aβ and Aβ, and Improves Memory Deficits, in the APPLon Mouse Model of AD

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Background: Pyroglutamate amyloid-beta peptides (pGlu-Abeta) are particularly neurotoxic forms of Abeta, and they accumulate with full-length Abeta peptides in Alzheimer's disease (AD) brains. pGlu-Abeta peptides are N-terminally truncated forms of full-length Abeta peptides (flAbeta(1-40/42)) with modification of the N-terminal glutamate to form pGlu-Abeta(3-40/42). The significant presence of pGlu-Abeta in AD brains may be important in the development of AD because pGlu-Abeta initiates formation of oligomeric neurotoxic Abeta forms. Beta-secretase processing of amyloid precursor protein (APP) produces flAbeta(1-40/42), but it is not yet known whether the beta-secretase BACE1 or the alternative beta-secretase cathepsin B (CatB) participate in the production of pGlu-Abeta. Therefore, experiments examined the effects of gene knockout of these proteases on pGlu-Abeta and flAbeta brain levels, amyloid plaque load, and memory deficits in APPLon AD mice, which express APP-695 and have the wild-type (wt) β-secretase activity found in most AD patients.

Methods: APPLon mice with knockout of the CatB or BACE1 gene were generated, and were assessed for memory deficits by the Morris water maze test. Brain extracts were measured for levels of pGlu-Abeta and flAbeta peptides by ELISAs, and amyloid plaque load was assessed by quantitative immunohistochemistry.

Results: Knockout of the CatB gene reduced brain levels of pGlu-Abeta(3-40/42), flAbeta(1-40/42), and pGlu-Abeta/Abeta plaque load in APPLon mice. Expression of the CatB gene increased levels of pGlu-Abeta and Abeta peptides, as well as amyloid plaque load. Substantial improvements in memory deficits resulted from knockout of CatB. But knockout of the BACE1 gene had no effect on levels of these Abeta forms and had no effect on memory in the APPLon mouse model of AD.

Conclusion: CatB participates in the production of pGlu-Abeta and flAbeta, and the absence of the CatB gene improves memory deficits in the APPLon AD mouse model. These findings suggest that inhibitors targeting CatB will be useful in therapeutic treatment of AD patients.

Theme: Therapeutics, Preclinical,