Cathepsin S : A Novel Therapeutic Target for Alzheimer’s Disease

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Chronic inflammation in response to neuronal damage is thought to accelerate and potentially underlie disease progression in AD (AD). Here, we assessed the therapeutic potential of Cathepsin S as a new molecular target for the treatment of AD. Cathepsin S is a cysteine protease exhibiting both extra- and intracellular activities whose expression is largely confined to microglia. By regulating a step in MHC class II antigen presentation, cathepsin S play an important role in modulating immunoregulatory processes. In addition to the roles as inflammatory mediators, inhibition of cathepsin S could also potentially affect a number of cellular processes involved in protein proteolysis and lysosomal function, which have implication in AD pathology such as amyloid and tau. Thus, modulating activity of cathepsin S might provide therapeutic benefit to treat or slow the disease progression through modulation of specific element of inflammation and protein proteolysis.

With an aim of assessing the therapeutic potential of cathepsin S, we administered the cathepsin S inhibitor VBY50365 in the Thy1-APP(PS1ΔE9) mouse model of AD. Chronic administration of VBY50365 lead to improvement in cognitive deficits and pathology related to AD. This data suggest modulation of cathepsin S activity might be a novel therapeutic strategy for the treatment of AD.

Method

In vitro Enzyme Potency and Selectivity

Potency and selectivity of VBY50365 was evaluated on a panel of proteases listed in in vitro enzyme inhibition assays. All enzymes were human in origin except pancreatic elastase which was porcine. Enzyme reactions were run in conditions where substrate was equal to or less than the Michaelis constant, K_m and the resulting dose response curves were used to determine IC_50 of enzyme inhibition.

In vivo transgenic AD mouse model study

The effects of the CatS inhibitor were evaluated in the Thy1-APP(PS1ΔE9) mouse model of AD. Using a 2x2 factor design, 6 month old male transgenic mice and their non-transgenic littersmates received 100 mg/kg/day of the cathepsin S inhibitor VBY50365 or vehicle daily until 7.5 months of age. Functional outcomes of VBY50365 treatment on behavioral deficits were assessed at multiple time points post dosing through a battery of cognitive behavioral assays including activity chamber, Y-maze, passive avoidance, and fear conditioning. After behavioral testing, mice were sacrificed and brain tissue were harvested and used to assess the effects of VBY50365 on biochemical assessments.

Figure 1. In vivo transgenic AD mouse study Design

Results

Inhibition of Cathepsin S activity restores cognitive deficits

A. Y-Maze

B. Passive Avoidance

C. Fear Conditioning

Figure 4. VBY50365 reverses spatial memory deficits observed in Thy1-APP(PS1ΔE9) mice in the Y-maze (A) (*p<0.05, **p<0.01 by t-test) with similar trends for restoration of memory deficits observed in passive avoidance (B) and fear conditioning (C) memory test.

Inhibition of Cathepsin S activity reduces neuroimmune response

Figure 5. A quantitative analysis of the microglia marker iba-1 staining revealed that VBY50365 reduces microglia staining (iba-1) in cortex (RS) and hippocampus (DG).

Working in Progress

Cathepsin S and synaptic degeneration

Figure 6. Thy1-APP(PS1ΔE9) mice have synaptic degeneration in CA3 as measured by quantitative synaptophysin immunoreactivity.

Conclusion

• Cathepsin S is strongly implicated in AD pathology.
• Selective inhibition of cathepsin S activity lead to restoration of cognitive deficits associated with AD and reduced microglial activation in the CNS.
• Modulation of cathepsin S activity may provide therapeutic benefit in AD.

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