Diagnostic Potential of Aβ-clearance Intermediates in Elderly Subjects at Risk for Alzheimer's Disease

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Research question and background

Aβ peptides are continuously and abundantly produced from APP by β- (BACE) and γ-secretases in both healthy and Alzheimer disease (AD)-afflicted brain tissues. It is still unclear whether alterations in Aβ production or clearance occur in sporadic cases of AD [1]. Aβ is a heterogeneous mixture of peptides having different solubility, stability, biological and toxic properties. Secretases generate a variety of peptides via cleavage of APP (i.e., Aβ43, Aβ42, Aβ40, Aβ38, Aβ37), and even smaller variants are detected in cell culture and body fluids [2]. Routinely, a pattern of Aβ peptides including Aβ34, 37, 38, 39, 40 and 42 is detectable [3]. While Aβ38 is only derived from γ-secretase cleavage [2], we and others have shown that Aβ34 can also be generated as the result of BACE-mediated cleavage of both Aβ40 and 42 [4]. In a recent study, it has been suggested that the degradation of Aβ40 and 42 to Aβ34 is the rate-limiting step in Aβ- clearance [5].

Methods and tissues used

In the current project we are investigating the diagnostic potential of Aβ-clearance products in patients with mild cognitive impairment (MCI) and AD. We have recently generated a monoclonal, neo-epitope antibody specific for Aβ34, which recognizes Aβ34 with a high affinity in the lower picomolar range, and established an enzyme-linked immunosorbent assay based on this antibody. It is highly suitable also for Western Blot analysis as well as in immunohistochemistry. In a small pilot-study (unpublished data from our lab) we found that Aβ34 is significantly elevated in CSF samples of patients with MCI. These results suggest that during MCI there is elevated Aβ-clearance activity while this process might become impaired with the progress of AD pathogenesis. In order to get a clear picture of the mechanisms involved in Aβ34-production, we are performing a thorough biochemical and immunohistological analysis of patients afflicted with AD and MCI.

We received frozen and paraffin-embedded tissue from non-demented controls, Alzheimer's disease with Braak stages 4 and 6, Alzheimer's disease with CAA at Braak stages 4 and 6—six samples each.

Results and conclusion

It is to early in the analysis to present data. We have sectioned the paraffin-embedded tissue and performed initial analysis with anti-Aβ antibodies and Thioflavin S staining. Unexpectedly, only little plaque deposition and CAA was observed. We are now working on optimizing the staining against Aβ34. Analysis of frozen tissue is ongoing.

References

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