Abundance of Aβ5-x like immunoreactivity in transgenic 5XFAD, APP/PS1KI and 3xTG mice, sporadic and familial Alzheimer´s Disease.

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Research question and background

According to the modified amyloid hypothesis the main event in the pathogenesis of Alzheimer's disease (AD) is the deposition of neurotoxic amyloid β-peptide (Aβ) within neurons. Additionally to full-length peptides, a great diversity of N-truncated Aβ variants is derived from the larger amyloid precursor protein (APP). Vast evidence suggests that $Aβ_{x-42}$ isoforms play an important role triggering neurodegeneration due to its high abundance, amyloidogenic propensity and toxicity. Although N-truncated and $Aβ_{x-42}$ species have been pointed as crucial players in AD etiology, the $Aβ_{5-x}$ isoforms have not received much attention.

Methods and tissues used

Immunohistochemistry, brain material from Netherlands Brain Bank as well as from Uppsala and Helsinki.

Results and conclusion

The present study is the first to show immunohistochemical evidence of $Aβ_{5-x}$ in familial cases of AD (FAD) and its distribution in APP/PS1KI, 5XFAD and 3xTG transgenic mouse models. In order to probe $Aβ_{5-x}$ peptides we generated the AB5-3 antibody. Positive plaques and congophilic amyloid angiopathy (CAA) were observed among all the FAD cases tested carrying either APP or presenilin 1 (PS1) mutations and most of the sporadic cases of AD (SAD). Different patterns of $Aβ_{5-x}$ distribution were found in the mouse models carrying different combinations of autosomal mutations in the APP, PS1 and Tau genes. All of them showed extracellular Aβ deposits but none CAA. Additionally, they were all affected by a severe amyloid pathology in the hippocampus among other areas. Interestingly, neither 5XFAD nor APP/PS1KI showed any evidence for intraneuronal $Aβ_{5-x}$.

Different degrees of $Aβ_{5-x}$ accumulations can be found in the transgenic AD mouse models and human cases expressing the sporadic or the familial form of the disease. Due to the lack of intracellular $Aβ_{5-x,}$ these isoforms might not be contributing to early mechanisms in the cascade of events triggering AD pathology. Brain sections obtained from SAD cases showed higher $Aβ_{5-x}$–immunoreactivity in vascular deposits than in extracellular plaques, while both are equally important in the FAD cases. The difference may rely on alternative mechanisms involving $Aβ_{5-x}$ peptides and operating in a divergent way in the late and early onset forms of the disease.