INTRACELLULAR PRESENCE OF PYROGLUTAMATE MODIFIED AMYLOID BETA AGGREGATES IN NEURONS AND ASTROCYTES

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Introduction: Amyloid beta (Aβ) oligomerization and accumulation have an important function in the pathology of Alzheimer's disease. Aβ however is not a single entity. In the brain multiple variants can be detected. These variants are truncated at their N- or C-termini and/or harbor several posttranslational modifications. All these changes alter the chemical structure of the amyloid beta peptides resulting in the generation of peptides with different properties. A variant that has recently been show to be important in early pathogenesis of AD is the pyroglutamate (pE) modified Aβ3-42.

Aims: In this study we analyzed the role of the Aβ(pE)3-42 oligomers in the pathogenesis of this disease.

Methods: An antibody was raised against oligomers of Aβ(pE)3-42. After extensive characterization, this antibody was used to immunohistochemically stain post-mortem brain tissue of control and AD patients.

Results: Characterization of this antibody confirmed that it only recognizes early intermediates of aggregated Aβ(pE)3-42 species, while monomers of Aβ(pE)3-42 are not recognized. In human brain tissue, this conformation specific antibody shows a granular staining in neurons and in astrocytes and double labeling proved that these aggregates are present in the lysosomes. Moreover immunohistochemistry showed an age and AD pathology related increase of these aggregates.

Conclusions: These data indicate that intracellular accumulation of oligomers might be involved in the pathogenesis of this disease. Based on our observations, we hypothesize that an age-dependent decline in the lysosomal degradation capacity might explain the accumulation of these aggregates in the lysosome and eventually contributes to cell death.