DISENTANGLING THE CONTRIBUTION OF TAU AND ABETA PATHOLOGIES IN TRANSGENIC MODELS OF ALZHEIMER'S DISEASE

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AIMS: Amyloid-beta (Abeta) deposits and intraneuronal hyperphosphorylated tau are major pathological hallmarks of Alzheimer's disease (AD). The coexistence of these aggregates in AD brains leads to synaptic dysfunction, neuronal loss and cognitive decline. Failures in protein homeostasis, along with defective glial responses, have been identified as pathological mechanisms linked to this disorder. Thus, our main objective is to better understand the differential impact of Abeta- and tau-aggregates to these processes in the hippocampus of AD models.

METHODS: We analyzed APP- (APPSL/PS1M146L) and Tau- (ThyTau22 and hP301S) based models from 2 to 18 months of age. Tau and Abeta pathologies were assessed by western blotting and immunohistochemistry. Confocal microscopy was used to study microglia/aggregates relationship. Levels of synaptic proteins, autophagy and inflammatory markers were determined by quantitative PCR, WB and immunohistochemistry.

RESULTS: Tau and Abeta pathologies initiated as early as 2 months of age and increased progressively with aging. Even though only APP/PS1 hippocampus showed dystrophic neurites positive to proteostatic and presynaptic markers, their protein levels were altered in both types of models from 6-9 months compared to age-matched WT mice. Inflammatory markers and microglial reactivity were barely increased in the hippocampus of ThyTau mice in contrast to P301S and APP/PS1 mice which displayed a prominent microglial response.

CONCLUSIONS: Clarifying the effects of Abeta and tau separately would indeed enable the development of novel therapeutic strategies and drugs targeting pathways related to these proteinopathies.

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