TAU BECOMES LOCALLY MISSORTED INTO DENDRITES AFTER EXPOSURE TO ABETA-OLIGOMERS, WITH CONCOMITANT LOCAL CA++ ELEVATION, SPINE LOSS, TAU PHOSPHORYLATION, DESTRUCTION OF MICROTUBULES, AND NEUROFILAMENT INVASION

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Introduction: Aggregation of Abeta and Tau are hallmarks of AD, whereby Abeta is considered toxic for neurons and Tau a downstream target.

Aims: Characterize the cascade from extracellular Abeta-oligomers to Tau pathology in neurons.

Methods: We studied hippocampal neurons for early changes of endogenous Tau induced by Abeta-oligomers.

Results: Initial events include missorting of endogenous Tau into soma and dendrites in a subset of neurons, in contrast to axonal sorting in normal neurons. Missorted dendrites show depletion of spines, elevated phosphorylation of Tau at several sites diagnostic of AD-Tau (notably 12E8 epitope, pS262/pS356, and AT8 epitope, pS202/pT205), and local elevation of some kinase activities (e.g. MARK, cdk5). These local effects occur without major global changes in Tau, tubulin, kinase levels or activities. Missorting affects not only Tau, but also other axonal markers such as neurofilaments, and correlates with a dramatic local decrease of microtubules and mitochondria (~80%). The Abeta-induced effects on depletion of microtubules and mitochondria, Tau missorting, and spine loss are prevented by the microtubule-stabilizer taxol, indicating that Abeta-induced microtubule destabilization and corresponding traffic defects are key factors in incipient degeneration. By contrast, the rise in Ca++ levels, kinase activities, and Tau phosphorylation cannot be prevented by taxol. Local changes similar to those of Abeta can be evoked by cell stressors, e.g. H2O2, glutamate, serum deprivation.

Conclusions: Data suggest that Abeta-oligomers induce changes in dendritic signalling pathways similar to those induced by other cell stressors. One could call Abeta-oligomers cell stressors.

- Support: MPG, DFG, Breuer-Foundation, Metlife-Foundation, EU-Memosad.