Involvement of Neurons, Astrocytes and Oligodendrocytes in Tau Seeding and Spreading in Alzheimer's disease and Tauopathies

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Human tau seeding and spreading occur following intracerebral inoculation of brain homogenates obtained from Alzheimer's disease (AD) and tauopathies in transgenic mice expressing wild or mutant tau, and in wild-type mice. This presentation is focused on the patterns of tau seeding, the cells involved, and the characteristics of tau following intracerebral inoculation of homogenates from Alzheimer's disease (AD) primary age-related tauopathy (PART: neuronal 4Rtau and 3Rtau), pure aging-related tau astrogliopathy (ARTAG: astroglial 4Rtau with thorn-shaped astrocytes TSAs), globular glial tauopathy (GGT: 4Rtau with neuronal tau and specific tau inclusions in astrocytes and oligodendrocytes, GAIs and GOIs, respectively), progressive supranuclear palsy (PSP: 4Rtau with neuronal inclusions, tufted astrocytes and coiled bodies), Pick's disease (PiD: 3Rtau with characteristic Pick bodies in neurons and tau containing fibrillary astrocytes), and frontotemporal lobar degeneration linked to P301L mutation (FTLD-P301L: 4R familial tauopathy). For these purposes, young and adult WT mice were inoculated unilaterally in the hippocampus or the lateral corpus callosum with sarkosyl-insoluble fractions and sarkosyl-soluble fractions from tauopathies, and were killed at variable periods of from three to seven months. Tau seeding occurs in the ipsilateral hippocampus and corpus callosum, and spreads to the septal nuclei and contralateral corpus callosum. Tau deposits are found mainly in neurons and oligodendrocytes, and in threads which contain phosphorylated tau, tau with abnormal conformation, and 3Rtau and 4Rtau independently of the type of tauopathy, but not truncated tau at aspartic acid 421. Moreover, tau deposits co-localize with active (phosphorylated) tau kinases p38 and ERK½, indicating active tau phosphorylation of murine tau. In conclusion, seeding and spreading of human tau in the brain of WT mice involves neurons and glial cells, thereby supporting the idea of a primary role of astrogliopathy and oligodendrogliopathy in the progression of tauopathies. This process is particularly important in the white matter, which acts as a corridor of tau seeding and spreading in tauopathies. Human tau inoculation modifies murine tau metabolism with the production and deposition of 3Rtau and 4Rtau, and by activation of specific tau kinases in affected cells.