Structural and functional changes in the hippocampus of tau transgenic mice

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Alzheimer's disease (AD) brain is characterized by an extensive plaque and tangle pathology. Plaques consist of amyloid peptide deposits, while tangles are intracellular accumulations of hyperphosphorylated tau. Neurofibrillary tangles correlate well with the memory impairment in AD. Considerable diversity in tau protein is generated by alternative splicing, and by many phosphorylation sites. Mutations in tau cause frontotemporal dementia, associated with tangle pathology and increases in the 4 repeat isoform. Extensive tau phosphorylation is also found in AD. One of the areas affected in AD is the hippocampus, well-known for learning. In this area, also in adult brain, neurogenesis continues and may be related to memory formation. Several factors stimulate neurogenesis, and besides learning most notably, damage to the hippocampus. In AD, adult proliferation appears to be altered, since cell cycle markers and mitotic phosphoepitopes, normally only present during development, are found in the hippocampus of AD patients.
To study the effect of tau on neurogenesis, we quantified proliferation i n the hippocampus of two tau mutant mouse strains expressing human tau-4R and hyperphosphorylation. The immunocytochemical proliferation markers Ki-67, BrdU and Doublecortin were used. Our results show that hippocampal proliferation, cell survival, and the migration of newly formed neurons, is significantly increased in the dentate gyrus of one of these transgenics.
In parallel, apoptosis was reduced. These results fit with the increased volume and cell number of the hippocampus found in these mice. Since these effects are only seen in mice expressing human tau-4R, we suggest that changes in tau-isoforms affect neurogenesis, which then leads to an altered cell morphology. To define how these morphological changes correlate with functioning, we studied hippocampal plasticity at long and short term. Preliminary data show that plasticity is impaired in these mice.
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I would like to be in session Neuroscience 2 (thursday)