Co-expression of Virally Induced P301L Tau and Transgenic β-Amyloid in APP Mice as Model of Alzheimer’s Disease to Closer Mimic Human Pathology

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BACKGROUND

Major histopathological features of Alzheimer’s disease (AD) are: (1) Neurofibrillary tangles (NFT) of hyperphosphorylated Tau aggregates, and (2) senile plaques of insoluble β-amyloid (Aβ). To generate a mouse model that combines these two hallmarks we virally induced expression of P301L human Tau in the hippocampus of APP/ mice by stereotactic injection. Human P301L Tau increases NFT and is the main cause of Frontotemporal Dementia with Parkinsonism-17 (FTDP-17) (Hutton et al., 1998, Spillantini et al., 1998).

We investigated spatiotemporal patterns of histopathology with a focus on potential interaction between both markers that are associated with human AD pathology.

MATERIALS AND METHODS

Recombinant adeno-associated virus serotype 9 (AAV9) with human P301L Tau gene under the control of CMV promotor was injected into the hippocampus of 3 months old male APPSL mice (AP: -1.8; ML: +1.4; DV: -1.4).

- Immunohistochemical and biochemical analyses were performed using:
  - human Tau (Tau 13, Enzo Life Sciences)
  - hyperphosphorylated Tau: AT100 (Pierce Biotechnology), AT180 (Thermo Scientific), Ser262 (MBL), PHF-13 (Cell Signaling), EPR2603 (abcam)
  - aggregated beta amyloid (LOC, abcam)
  - APP (6E10, BioLegend)

RESULTS

Stable expression of human P301L Tau in hippocampus

- Cleavage of human APP located in neostriatum 7 months after injection.
- Expression was confirmed throughout entire hippocampus formation within 3 weeks.
- Surveying brain sections with antibodies AT100 and AT180 showed Tau expression in the neostriatum with high concentration at weeks 3.
- Tau deposits were observed in neostriatum with high concentration at weeks 3.
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HIGH LEVELS OF HYPERPHOSPHORYLATED TAU ARE ASSOCIATED WITH PATHOLOGICAL PHOSPHORYLATION AT AD-RELATED RESIDUES

- The expression of hyperphosphorylated Tau was detected by antibodies AT100, AT180 and EPR2603. AT100 and AT180 are phosphorylated motifs frequently found in AD brain but not in healthy individuals.
- As shown in Figure 2, Tau expression was evident throughout the entire hippocampal formation within 3 weeks.
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CONCLUSION

High levels of virally induced P301L Tau are present throughout the entire hippocampus of APPSL mice. Tau expression is stable for at least 8 months post injection, providing a long period for drug testing and for investigating interaction of Aβ and Tau. Of note, phosphorylation of several Tau residues typical for human AD has been confirmed in this new mouse model. While analyses are ongoing, we believe these animals constitute a promising new model for drug development and compound testing.