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Inefficient induction and spread of seeded tau pathology in P301L mouse model of tauopathy suggests inherent physiological barriers to transmission

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Intercellular prion-like transmission of misfolded and aggregated tau protein along interconnected anatomic pathways is thought to contribute to the etiology of tauopathies, such as Alzheimer's disease (AD) [4]. Indeed, the observation that synthetic tau fibrils and AD patient brain homogenates are capable of inducing robust tau pathology in tau transgenic mice strongly support the hypothesis that exogenous tau can trigger tauopathy by prion-like templating and transmission [1–3,6]. Transmission of tauopathy seems to depend on the molecular conformation of the exogenous seeds [8]. Therefore, characterizing the differential seeding and transmission properties of tau conformers will allow us to determine optimal therapeutics against tauopathies.

Here, we evaluated the seeding and transmission properties of pre-fibrillized wild type K18 tau fragment which contains all four microtubule binding domains of the longest tau isoform and retains the amyloid fibril core [9]. Since sonication potentiates prion seeding [7], we investigated the seeding properties of K18 fibrils sonicated either 1) in a low-power water bath sonicator ("Bath") yielding typical shorter fibrillar preparations or 2) with a metal probe sonicator ("Probe") resulting predominantly in amorphous aggregates as observed by negative staining electron microscopy (Supplementary Figure 1). Using HEK293T cells overexpressing tau, we demonstrated that both types of sonicated K18 fibrils could efficiently induce intracellular detergent-insoluble tau inclusions in the presence of lipofectamine (Supplementary Figure 2). Next, we tested whether sonicated K18 fibrils induce tauopathy in homozygous JNPL3 tau transgenic mice expressing P301L tau (hP301L) (Supplementary Table 1) [5]. The protracted nature of disease progression makes

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the hP301L mice an excellent primed model to study seeding and transmission of tauopathy [5]. Sonicated K18 fibrils was bilaterally injected in the hippocampus of 2-month old hP301L mice and analyzed after 4 months. In female hP301L mice, probe-sonicated K18 fibrils, but not bath-sonicated fibrils, induced limited AT8 and PHF1 immunoreactive tau pathology directly at the injection site (hippocampus) and in the neuro-anatomically connected entorhinal cortex (arrows, Figure 1; Supplementary Figure 3). Tau pathology, typically observed in aged hP301L mice, was observed in the brainstem and midbrain of all mice, irrespective of injection. Male hP301L mice similarly injected in the hippocampus with probe-sonicated K18 fibrils failed to show any induction of tau pathology (Supplementary Figure 4). Since hP301L mice develop early spinal cord and brainstem tau pathology [5], we reasoned that if K18 fibrils trigger templated tau protein transmission depending on focal priming, injection of seeds in the gastrocnemius muscle (IM) or cisterna magna (ICM) might induce or potentiate tau pathology following projections along the spinal cord and brainstem. IM or ICM injection of sonicated K18 (water-bath and probe sonicated) fibrils did not result in increased tau pathology in the CNS, suggesting inefficient peripheral to central transmission of tauopathy (Supplementary Figures 5–6).

In summary, we have demonstrated that though a) synthetic K18 aggregates display robust seeding in vitro, b) intra-hippocampal administration of probe-sonicated K18 fibrils lead to limited induction of tau pathology, and c) peripheral administration of K18 tau does not induce CNS tau pathology in hP301L mice.

Our data suggests that significant physio-chemical barriers, dependent on factors such as physical proximity to the injection site and conformation of seeds used, regulates induction of tau pathology in hP301L mice. Our studies seemingly differ from a recent observation of robust tauopathy induction in P301L transgenic mice using K18/PL seeds [6] but these discrepancies may be explained by differences in the type (wild type K18 or K18/PL) and conformation of tau seeds used. Such intriguing observations raise further notions regarding differential transmission properties of tau conformers as well as the acceptor mouse model, ostensibly contributing to distinct physio-chemical properties of tau seeds as suggested by other groups [8]. Based on our data, we speculate that tau inclusion pathology follows a non-stochastic process where conformationally distinct misfolded tau fibrils with specific clinico-pathologic properties display differential seeding potential, perhaps leading to phenotypic diversity of tauopathies [8]. Overall, K18 seeding and spread of tau pathology is an inefficient process in the hP301L primed tau mouse model, highlighting the complex nature of intercellular transmission of tauopathy. These findings should stimulate further studies in harnessing the endogenous mechanisms that can modify or even impede the induction and transmission of tau pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Hippocampal injection of probe-sonicated K18 induces limited tauopathy in female hP301L mice. hP301L mice were bilaterally injected in the hippocampus (arrowhead, top panel) with K18 fibrils sonicated using a bath or probe sonicator, or PBS and analyzed after 4 months. The columns display representative AT8 immuno-stained images from selected sites: 1, entorhinal cortex, 2, hippocampus (CA2–3), 3, midbrain, and 4, brainstem (boxed areas, top panel). Arrows mark AT8 immuno-positive intracellular tau inclusions in the cortex and hippocampus of mice injected with probe-sonicated K18. $n=3-5/\text{group}$. Scale bar, 25 μm .