Review

Biological Psychiatry

Propagation of Tau Pathology: Integrating Insights From Postmortem and In Vivo Studies

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ABSTRACT

Cellular accumulation of aggregated forms of the protein tau is a defining feature of so-called tauopathies such as Alzheimer's disease, progressive supranuclear palsy, and chronic traumatic encephalopathy. A growing body of literature suggests that conformational characteristics of tau filaments, along with regional vulnerability to tau pathology, account for the distinct histopathological morphologies, biochemical composition, and affected cell types seen across these disorders. In this review, we describe and discuss recent evidence from human postmortem and clinical biomarker studies addressing the differential vulnerability of brain areas to tau pathology, its cell-to-cell transmission, and characteristics of the different strains that tau aggregates can adopt. Cellular biosensor assays are increasingly used in human tissue to detect the earliest forms of tau pathology, before overt histopathological lesions (i.e., neurofibrillary tangles) are apparent. Animal models with localized tau expression are used to uncover the mechanisms that influence spreading of tau aggregates. Further, studies of human postmortem-derived tau filaments from different tauopathies injected in rodents have led to striking findings that recapitulate neuropathology-based staging of tau. Furthermore, the recent advent of tau positron emission tomography and novel fluid-based biomarkers render it possible to study the temporal progression of tau pathology in vivo. Ultimately, evidence from these approaches must be integrated to better understand the onset and progression of tau pathology across tauopathies. This will lead to improved methods for the detection and monitoring of disease progression and, hopefully, to the development and refinement of tau-based therapeutics.

Keywords: Alzheimer's disease, Cerebrospinal fluid, Models, Positron emission tomography, Spreading, Tau

https://doi.org/10.1016/j.biopsych.2019.09.019

Tauopathies are a heterogeneous class of diseases characterized by cellular accumulation of aggregated tau. Alzheimer's disease (AD) is the most prevalent tauopathy, currently affecting approximately 50 million people worldwide (1). Whereas AD is also characterized by extracellular plaques composed of aggregated fibrillar amyloid-β (Aβ), other tauopathies such as corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Pick's disease, chronic traumatic encephalopathy (CTE), and aging-related tau astrogliopathy are primarily characterized by tau pathology (2,3). Interestingly, the morphology of the cellular aggregates and affected cell types can vary between these diseases. For example, while AD mainly features neurofibrillary tangles (NFTs) and neuropil threads within neurons, together with dystrophic neurites surrounding Aβ plaques (4), PSP and CBD present with prominent astrocytic and oligodendroglial tau pathology (Figure 1) (3). The different tauopathies also have distinct anatomical distribution of pathology and present as unique clinical syndromes (3). Owing to its close correlation with neurodegeneration and cognitive symptoms (5,6), there is a growing interest in the biology of tau propagation throughout the human brain in different tauopathies. This review provides an AD-focused overview of the literature, with the goal of integrating the existing knowledge obtained from human postmortem studies, animal models, tau positron emission tomography (PET), and fluid biomarkers.

TAU PATHOBIOLOGY

Tau protein is the major constituent of NFTs in AD (7–10) and the lesions found in PSP and Pick's disease (11–13). Tau is an abundant axonal microtubule–binding protein with a variety of physiological functions (14). It can be subdivided into several domains: the structurally disordered N-terminal, the proline rich mid-domain, and the highly conserved C-terminal domain (Figure 2) (15–17). The C-terminal half of the protein contains the microtubule binding repeats, which are partly incorporated into the core of tau filaments (17–20). Tau protein is encoded by the *MAPT* gene on chromosome 17q21.31, and various mutations in this gene have been linked to an increased risk of tau pathology and clinical symptoms, thereby strongly indicating tau pathology as causal to neurodegeneration (21–23). The *MAPT* gene messenger RNA in the central nervous system can be alternatively spliced to encode 6 isoforms of the tau protein, containing either 0, 1, or 2 N-terminal inserts and 3 or 4

ISSN: 0006-3223

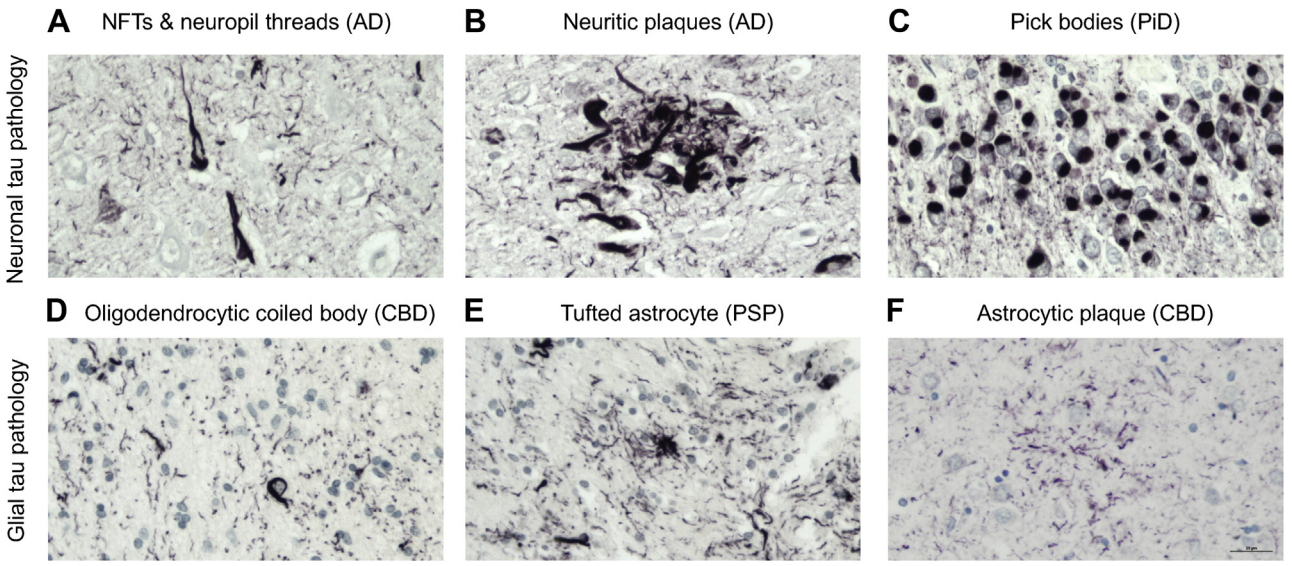

Figure 1. Heterogeneity of tau pathology in different tauopathies. All figures show AT8 (p202/205) staining on paraffin sections. **(A)** Neurofibrillary tangles (NFTs) and neuropil threads in the hippocampus of a patient with Alzheimer's disease (AD). **(B)** Neuritic plaques in the hippocampus of a patient with AD. **(C)** Pick bodies in the granular cells of the hippocampus of a patient with Pick's disease (PiD). **(D)** Oligodendrocytic coiled body in the caudate nucleus of a patient with corticobasal degeneration (CBD). **(E)** Tufted astrocytes in the caudate nucleus of a patient with progressive supranuclear palsy (PSP). **(F)** Astrocytic plaques in the caudate nucleus of a patient with CBD.

microtubule binding repeats (24,25). The difference between the 3-repeat (3R) and 4-repeat (4R) isoforms is that the 4R isoform includes the second repeat encoded by exon 10, which is spliced out in 3R tau. Tau protein is subject to many post-translation modifications, such as phosphorylation, acetylation, and truncation (14). Interestingly, it was already discovered early on that the tau proteins incorporated in the fibrils are hyperphosphorylated (25). The precise role of post-translation modifications in the initiation of tau pathology is currently unresolved. However, several studies indicate that N- and C-terminal truncation of tau may be an important early event in tangle formation and that truncated tau potently induces neurofibrillary degeneration in transgenic animals (26–28).

Insights into structural features of tau that are involved in the aggregation process have been obtained by studying recombinant tau in vitro. Although a natively unfolded protein, tau does appear to have a global physiological structure in which the C-terminal folds over the microtubule binding repeats and both ends of the molecule approach each other (29). The microtubule binding repeats of tau contains 2 hexapeptides that can form intermolecular β-sheet rich structures: aa275-280 (VQIINK) in R2 and aa306-311 (VQIVYK) in R3 (30,31). Under pathological conditions, tau can adopt an abnormal conformation that exposes these residues and increases its propensity for self-aggregation (32,33). Physiological tau monomers can be incorporated into aggregates; this process is known as templated misfolding or seeded nucleation and results in the rapid elongation of aggregates (34). The seeding process starts with the misfolding and aggregation of tau monomers, which then form the building unit for the formation of oligomers and ultimately highly structured fibrils that are insoluble in detergents such as sarkosyl (34,35). In AD, these tau filaments can take the form of paired helical filaments and straight filaments, which accumulate as a mixture within the cell in the form of NFTs (36).

Tau research is increasingly focused on the highly reactive detergent-soluble oligomers, rather than on the relatively inert, larger detergent-insoluble fibrils (37). In AD, neurons with NFTs can survive for decades (38). Additionally, neuronal loss correlates with but exceeds NFTs in AD (39,40). Furthermore, suppression of tau overexpression in a mouse model with aggressive tauopathy led to rescue of neurodegeneration and cognitive deficits. Interestingly, NFTs continued to develop, indicating that the toxicity mainly originates from soluble tau that is not sequestered by insoluble tau fibrils (41). Indeed, overexpression of an aggregation-prone version of tau rapidly induced the formation of Gallyas-positive NFTs but reduced the neurotoxicity of soluble tau (42). It is still conceivable that larger tau aggregates may exert toxicity by taking up space in the crowded environment of the cell. However, the soluble oligomers can easily diffuse throughout the cell, interact in a nonphysiological manner with a wide range of cellular proteins, and cause synaptotoxicity (43).

Smaller tau species can also propagate from cell to cell and seed physiological tau in healthy neurons (44–46). Both physiological and aggregated tau are secreted into the interstitial fluid, with this process increased by synaptic activity (47–50). The current in vitro evidence suggests that tau secretion occurs via 1) release from synaptic vesicles (51), 2) secretion in extracellular vesicles such as exosomes (52), 3) direct translocation across the membrane (53), and/or 4) transport through tunneling nanotubes (54). Tau can be taken up from the extracellular space via additional mechanisms: 1) bulk endocytosis (55), 2) macropinocytosis by heparan sulfate proteoglycans (56), and/or 3) clathrin-mediated endocytosis (57,58). After tau seeds enter the neuron, they can leak via damaged vesicles into the cytosol and seed physiological monomers to propagate the pathological process (59,60). Additionally, microglia and astrocytes can phagocytose

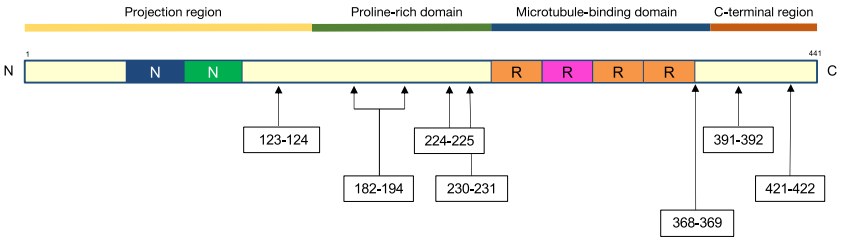

Figure 2. Domains of tau and identified truncation sites in the brain and cerebrospinal fluid tau. Tau protein is depicted here as the longest isoforms (2N4R). Tau protein can be subdivided into the projection region at the N-terminal, the proline rich mid-domain, the microtubule-binding domain, and the distal C-terminal. Each of 6 possible tau isoforms contains 0, 1, or 2 N-terminal inserts (blue and green boxes with N), and either 3 or 4 repeats (orange and pink boxes with R), as R2 (pink) can be spliced out in 3-repeat isoforms. The amino acid numbers below depict examples of identified truncation sites. These truncation sites may play an important role in the pathogenesis of tau pathology and detection of tau in bodily fluids.

extracellular tau and are involved in tau spreading (61–63). The process of tau spreading is now hypothesized to underlie the progression of tau pathology throughout the brain (Figure 3).

FINDINGS FROM POSTMORTEM PATIENT STUDIES USING IN VITRO BIOSENSOR ASSAYS AND STRUCTURAL BIOLOGY

A seminal postmortem study in 1991 described the stereotypical appearance and progression of tau pathology in AD (64), which was later associated with the progression of cognitive symptoms (65). This pattern was developed into a staging scheme based on the histological detection of NFTs and subsequent cross-sectional comparisons between AD brain tissue at different disease stages and is widely used in the research field (64) (Figure 3). Beginning in the rostral medial temporal lobe (specifically the entorhinal cortex, Braak stage I/II), tau pathology is thought to then progress to limbic regions (Braak stage III/IV), including the hippocampus. Tau pathology ultimately reaches the neocortex (Braak stage V/VI), which is invariably associated with cognitive symptoms (65). The primary motor and sensory cortices can remain spared even at these stages. Tau-associated neurodegeneration of the entorhinal cortex is thought to lead to a functional disconnection of the hippocampal formation from the cortical association areas, a process that may underlie the cognitive symptoms in AD (66).

It is currently unclear why the entorhinal cortex is particularly vulnerable to tau pathology and neurodegeneration in AD. Tau pathology in AD always seems to affect the same cell type, i.e., the large excitatory pyramidal cells in layer II of the entorhinal cortex that project via the performant pathway to the hippocampus. It has been proposed that the regional vulnerability of these neurons in the entorhinal cortex stems from their high metabolic rate resulting from high dendritic complexity, long unmyelinated axons, high degrees of plasticity, and unique gene expression signature related to tau homeostasis (67–70). It is worth noting that tau pathology in the primary tauopathies starts in different brain regions and additionally affects glial cells. Recent progress, for example, has been made in staging the progression of astrocytic tau pathology in aging-related tau astrogliopathy (71). This raises the question of how and why selective regional vulnerability to tau pathology differs between different tauopathies. CTE is unique in this regard because the tau pathology is induced by external trauma, leading to individualized progression patterns, which start in the cortex and later progress to the hippocampus and other brain regions (72).

It was originally assumed that the progression of tau pathology throughout the rest of the brain was mediated by regional vulnerability. As mentioned previously, however, there is now accumulated evidence that tau aggregates can spread along neuronal connections and lead to templated misfolding in healthy cells (73). A sensitive Förster resonance energy transfer–based biosensor assay was developed by Mark Diamond and is now widely used to measure tau seeding in brain samples (74). Several studies that have compared neuropathology and tau seeding using this assay at different Braak stages in patients with AD have shown that tau seeding can be detected before overt tau pathology in the entorhinal cortex and connected neuroanatomical regions (75,76). Furthermore, seed-competent tau was isolated from white matter tracts, indicating that tau seeds can be transported along neuronal connections (77). The same study also detected seed-competent tau in synaptosomes from patients with AD, which were isolated from brain regions that have not yet demonstrated tau pathology (77). Though some authors have hypothesized that tau pathology starts in the locus coeruleus, no tau seeding was observed in this area in early Braak stages (76). Two recent studies used size-exclusion chromatography to isolate a high-molecular-weight tau species from AD brain tissue and cerebrospinal fluid (CSF), which constituted only a small fraction of total tau but was highly seed competent and spread efficiently to other cells (78,79). Tau isolated from AD cases with Aβ plaque pathology was more seed competent than tau from a case without plaques; this could be experimentally explained by an increased proportion of high-molecular-weight tau in the presence of plaque pathology (80).

A recent study also used Förster resonance energy transfer–based cellular biosensor assay to demonstrate that primary microglia, derived from patients with AD or other tauopathies, secrete seed-competent tau into the extracellular space (63). The results of this study suggest that while microglia phagocytose extracellular tau, they seem unable to fully degrade it, secreting it back into the extracellular space; in this way, microglia may contribute to the propagation of tau pathology (63). The region-dependent differences in phagocytic capacity and the sensitivity of this process to aging (81,82) may provide a link between regional vulnerability and tau spreading.

As mentioned previously, there is considerable heterogeneity in tau pathology across tauopathies. Recent cryo-electron microscopy studies have provided unprecedented insight into how structural differences in aggregates may lead to these differences. Tau filaments extracted from the brain of a patient with AD showed that the core is located at residues

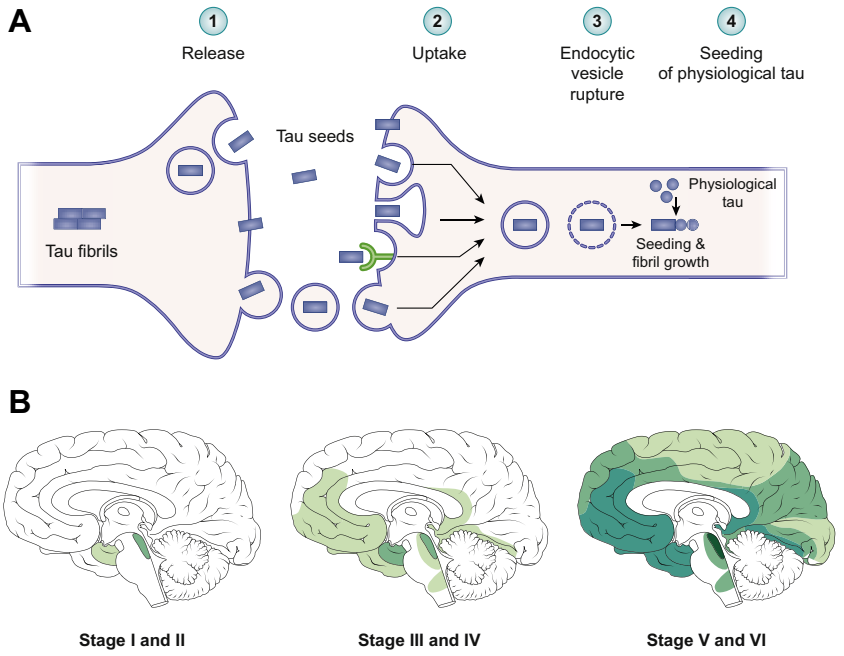

Figure 3. Propagation of tau pathology in Alzheimer's disease. **(A)** Mechanisms of tau spreading. 1) Release of tau into the extracellular space can occur via (from top to bottom) synaptic vesicles, direct translocation across the membrane, or extracellular vesicles. 2) Tau seeds can be taken up by healthy neurons via (from top to bottom) direct translocation across the membrane, macropinocytosis via heparan sulfate proteoglycans, bulk endocytosis, clathrin-mediated endocytosis, or fusion of extracellular vesicles with the plasma membrane. 3) Tau seeds that are taken up damage endocytic vesicles and thereby escape into the cytosolic compartment. 4) Tau seeds can then seed physiological tau, leading to the growth of the fibrils and propagation of the aggregation process. **(B)** Progression of tau pathology in AD as described by the Braak staging scheme using postmortem histology. Adapted with permission from Goedert *et al.* (150).

306 to 378 and that the configurations of paired helical filaments and straight filaments are slightly different (83). These residues are in the third and fourth repeats and part of the distal C-terminus, which may explain why both 3R and 4R tau can be incorporated into AD fibrils. The core of filaments from CTE is also located in the third and fourth repeats and thereby also consists of both 3R and 4R tau. However, CTE filaments also exhibit a structure distinct from AD fibrils, which encloses an additional density that is not connected to tau (84). This suggests that tau pathology in CTE may be caused by a cellular co-factor that promotes nucleation. In contrast, filaments derived from Pick's disease tissue adopt a radically different fold compared with AD or CTE, with the core between residues 254 and 378 and with an inability to incorporate 4R tau isoforms (85). These filaments also expose surface residues and phospho-epitopes that are distinct from AD filaments (85). Data on 4R tauopathies such as PSP or CBD are not yet available, but this will likely reveal yet another fold that excludes the 3R isoform. Important outstanding areas of investigation are what biophysical mechanisms cause tau to fold into distinct filaments, why this happens in distinct brain regions in different tauopathies, and what explains the presence or absence of glial tau pathology in the different tauopathies.

ANIMAL-BASED TAU SPREADING MODELS

Animal models of tauopathy have significantly advanced our understanding of tau pathobiology. In vivo spreading models can be roughly subdivided into 3 groups: 1) transgenic models, 2) viral vector models, and 3) seeding models (Table 1). Transgenic models overexpress human tau or its fragments that usually have mutations or amino acid deletions that increase the propensity of tau to aggregate. Transgenic models are widely used to study tau pathology, neuroinflammation, and tau-associated neurodegeneration (86). With an increased focus on tau spreading, transgenic models have been developed that selectively express the transgene in the entorhinal cortex (87,88). These models show spreading of human tau to neighboring and synaptically connected neurons, albeit only at advanced ages (12–21 months). For example, these models have been used to show that the presence of Aβ deposition accelerates the propagation of tau (89). Additionally, optogenetically increasing the activity of neurons in the entorhinal cortex speeds up spreading in this model (90).

Viral vector models are a practical improvement on transgenic spreading models, as they have been shown to induce spreading from the entorhinal cortex to the dentate gyrus in as little as 4 weeks after injection (61). For example, an adeno-associated virus (AAV) model has been used to show that when microglia were depleted, spreading was greatly diminished, thereby providing the first evidence that microglia play an important role in tau propagation (61). An advantage of AAV models is that they can be modified to express both human tau and fluorophores in a 1:1 ratio without fusing the proteins, thereby labeling the transduced cells (91). This method provides strong evidence for spreading, as it is unlikely that the synaptically connected cells were transduced by the AAV if they lack the fluorophore. AAV models can also be easily combined with existing transgenic models to study the mechanisms behind tau spreading, such as how proteins in pathways related to AD risk genes (e.g., DAP12) affect tau propagation (92).

Another interesting approach is to induce pathology and spreading by injecting aggregated tau isolated from the brains of transgenic animals or patients with tauopathy into mouse and rat tauopathy models (93–97). The introduction of existing

Table 1. Comparison of Different Widely Used Approaches to Study Spreading of Tau Pathology

Approach	Strengths	Limitations
FRET-based cellular biosensor assays (74–77)	Sensitive detection of tau seeding in brain tissue Allows for studying of cellular mechanisms of tau seed uptake	FRET signal is based on proximity of 2 tau molecules, not aggregation
Transgenic spreading mouse models (87–90)	No brain injection required	Overexpressed tau construct is artificial Very slow spreading (12–21 months)
Patient derived tau-based seeding models in mice (93,94)	Disease-specific conformation Recapitulates disease features not found in transgenic models	Requires brain injection Unclear which neurons take up tau, limits interpretation for spreading
Viral vector–based models in mice (91,92)	Rapid spreading Included fluorophore for determination of spreading	Requires injection of virus into the brain

FRET, Förster resonance energy transfer.

fibrils bypasses the need for nucleation, which is the rate-limiting step in the aggregation process. These fibrils can therefore immediately seed overexpressed human tau or physiological mouse tau. The spreading in these models was predominantly observed along neuronal connections, indicating that synaptic spreading is the dominant mode of tau propagation (98). In an interesting study, tau aggregates were isolated from seeded cells in vitro, then injected in animals, and the brain lysates were applied to cells again. By creating several tau "strains," this study demonstrated that the conformations of different types of tau aggregates can be stably maintained when repeating this process multiple times (99). A follow-up study also showed that different strains lead to unique cellular pathologies, aggregation properties, and anatomical spreading patterns (100).

Intriguingly, this strain hypothesis is now being extended by showing that tau isolated from patients with AD or patients with primary tauopathies (e.g., CBD, PSP) led to recapitulation of the original tau pathology in these diseases (e.g., histopathological morphology and cell-type specificity) (93,101). These models have now been refined to also induce tau pathology in wild-type mice. These studies show that AD-derived tau filaments are more aggressive than recombinant tau fibrils (102). In turn, tau filaments derived from CBD and PSP were more aggressive than AD-derived tau fibrils and also induced astrocytic or oligodendrocytic tau pathology (97). As tau pathology originates in different brain regions in, for example, AD, PSP, and CBD, it would be interesting to see if the neurons or glial cells in these areas give rise to the unique properties of the aggregates in these tauopathies.

When AD-derived tau filaments were injected in transgenic mice with Aβ plaque pathology, this led to the formation of all 3 major types of AD tau pathology in an animal model (i.e., NFTs, neuropil threads, and tau aggregates in dystrophic neurites) (103,104). This is noteworthy because the range of tau pathologies observed in AD has not been observed in previous transgenic mouse models expressing both Aβ and tau pathology (105). These studies therefore demonstrate that mouse models that are injected with patient-derived fibrils possess unique translational value in testing tau-based diagnostics and therapies. Indeed, a recent study described the induction and hippocampal spreading of tau pathology induced by injecting AD-derived tau filaments in a rat model overexpressing truncated tau (95). Given the bigger brain size of rats compared with mice, such models might prove useful for studying real-time tau spreading in vivo using PET imaging.

TAU PET IMAGING IN HUMANS

Though tau pathology is a challenging target for molecular imaging by means of PET (106)—owing to, for instance, the intracellular accumulation of tau and the varied ultrastructural conformations it can assume—remarkable progress has been achieved in this area over the past several years (107) (Figure 4). Using so-called first-generation tau ligands (e.g., [^{18}F]THK5351, [^{18}F]flortaucipir [AV1451], [^{11}C]PBB3), retention has been shown to be elevated in patients with AD, as compared with control subjects (108–110), with uptake patterns matching histopathology-derived staging schemes for tau (64,111,112). A drawback among first-generation tau ligands, however, is their off-target (nonspecific) binding to non–tau protein deposits, including iron, neuromelanin, and monoamine oxidase B. Novel tau ligands now entering the field (e.g., [^{18}F]MK-6240, [^{18}F]RO948, [^{18}F]GTP-1) appear to be less hampered by this (113,114); this awaits confirmation using larger samples (115). Studies in patients with primary tauopathies, such as CBD or PSP, while comparatively few in number, have also shown discrimination from control subjects and regional uptake relatively consistent with those expected in these diseases (109,116,117); however, oftentimes ligand retention appears in regions with known off-target binding, complicating accurate quantification. Given that existing ligands seem to bind preferentially to AD-type 3R/4R paired helical filament tau, however, it is likely the case that a range of novel compounds will ultimately be needed to cover the spectrum of primary tauopathies.

In the few studies hitherto addressing longitudinal tau PET in control subjects and patients with AD (118–122), increases in tau PET signal over time have been reported, with the greatest increases consistently being observed in individuals with dementia. In the largest of these to date (121), fairly uniform rates of tau accumulation were reported across brain regions, arguing against the histopathology-derived idea that tau pathology necessarily aggregates in a stepwise fashion. While not ruling out the concept that tau may spread transsynaptically, this finding does conflict with the idea that increases in the level of tau burden in the brain result from its spread from one unaffected area to another. This discrepancy between the thus far limited in vivo PET findings and histopathology may, however, be a reflection of the fact that current ligands lack extensive validation (123) or that the Braak tau staging scheme amounts to an extrapolation owing to its being grounded in cross-sectional autopsy data.

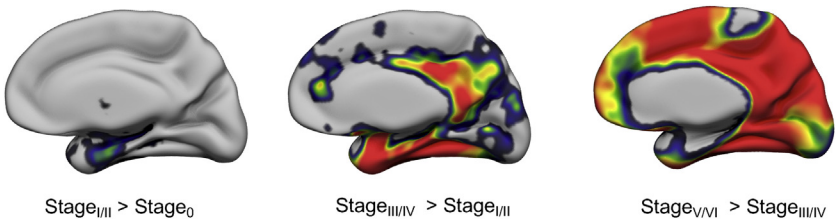

Figure 4. Progression of tau pathology measured by positron emission tomography. [^{18}F]Flortaucipir positron emission tomography–based stages of tau pathology among cognitively unimpaired and impaired subjects [for methods and original data, see Maass *et al.* (111)]. Images highlight the progression of tau from the medial temporal lobe to the parietal/frontal regions and, finally, the association cortices, corresponding to histopathologically established Braak stages. Adapted with permission from Maass *et al.* (111).

MEASURES OF TAU IN BODY FLUIDS

Core CSF biomarkers for AD include total tau (T-tau) and tau phosphorylated at threonine 181 (P-tau). Numerous clinical studies have consistently shown a marked increase in both AD and patients with mild cognitive impairment (124). These CSF biomarkers, together with CSF Aβ42, which reflects brain amyloidosis (125), are now included in research diagnostic criteria (126,127). In AD, elevated CSF T-tau is thought to reflect the intensity of neurodegeneration, while CSF P-tau reflects the phosphorylation state of tau, and likely tau pathology (128). However, with the exception of Creutzfeldt-Jakob disease, the concentrations of these markers are within the normal range in the majority of other tauopathies (129–132). This may be due to reduced secretion of tau into the extracellular space or simply an alternative processing of full-length tau in primary tauopathies that are not captured by the mid-domain immunoassays commonly used for assessment of AD. The possibility that increased CSF T-tau and P-tau concentrations in AD are not direct markers of neurodegeneration and tangle formation per se, but rather reflect increased tau secretion into the interstitial fluid in response to Aβ pathology (50) or other mechanisms that may lead to increased tau levels in the CSF, requires further study.

In AD, not all tau species present can be measured with the traditional mid-domain assays. Several studies suggest that tau is present as different fragments in CSF, with N-terminal and midregion tau representing the most abundant variants (133). This is especially evident in AD, while in primary tauopathies concentrations of truncated tau are surprisingly normal or even lower than those of control subjects (134,135). Assays targeting specific tau fragments (e.g., N-123, N-224, x-224, tau 368) have recently been developed and show promise as candidates to add to the AD and primary tauopathies biomarker panel (136).

The findings of tau in blood are less clear, particularly owing to the substantially lower concentration of tau in plasma compared with CSF. Plasma T-tau is slightly increased in AD compared with age-matched control subjects (137,138), but there is a substantial overlap between groups and a very poor correlation between plasma and CSF levels of T-tau (139). There are important confounders that explain these findings. First, although tau is brain enriched, substantial expression of tau from the salivary gland (140) and kidneys (141) that is seemingly unrelated to central nervous system pathology is observed. Second, the short half-life of tau in plasma (hours) compared with CSF (weeks) (142) makes it an unreliable biomarker of neurodegeneration. Recent developments have revealed increases in P-tau (143) and N-terminal tau (144), which are encouraging findings in need of replication.

Could detection of tau seeds in biofluids be used as a biomarker for tauopathies? A recently described technique called real-time quaking-induced conversion, which exploits the ability of prion protein to induce self-aggregation, has been used to develop a diagnostic CSF test for Creutzfeldt-Jakob disease (145). This method has now also been developed into a test to detect pathological forms of tau in CSF from patients with AD or other tauopathies (146,147). Seed-competent high-molecular-weight tau species have been detected in human CSF (78), but there is yet no established method in clinical laboratory practice.

CONCLUSIONS AND OUTLOOK

Interest in how tau pathology progresses through the brain has been a subject of research since the initial development of the staging scheme for tau pathology by Braak and Braak (64). The discovery of tau spreading in cellular and animal models has led to a surge of scientific efforts on this topic in the past decade (96). There has been significant progress in humanizing animal tauopathy models; by injecting patient-derived tau fibrils as seeds into rodent brains, the aggregation, histopathological lesions, and cell-type specificity of the patient can be recapitulated. Such models may provide better translatability to study the mechanisms of tau pathology in vivo and are increasingly used to test novel therapeutics (148,149). Important outstanding questions that can be studied with these models are, for example, how microglia, astrocytes, and other cell types are involved in the progression of tauopathy.

There have also been substantial developments in studying tau pathology at autopsy. Förster resonance energy transfer–based cellular biosensor assays can detect tau seeding activity before misfolding or hyperphosphorylation of tau, as detected by traditional histological means (e.g., MC1 or AT8 staining). Though these assays have mostly been applied to AD tissue, further studies in primary tauopathies are required to examine differences in regional vulnerability, and cell-to-cell spreading may vary among the tauopathies. As it is likely that neurons in certain anatomical regions are more vulnerable to accumulating tau pathology after taking up extracellular tau seeds, more studies are needed on the correlation between tau spreading and the transcriptional profile of vulnerable regions.

While the possibility to regionally map and quantify tau pathology in vivo has been introduced with tau PET ligands, more data are required for novel tau PET ligands, including comparative studies with CSF measures of tau. Measuring T-tau and P-tau in CSF has been possible for several decades and has constituted an important diagnostic tool; however, whether tau seeds in biofluids such as CSF could be used as clinically accessible diagnostic biomarkers needs to be established.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the European Union Horizon 2020 research and innovation program under Marie Skłodowska-Curie Grant No. 676144 (Synaptic Dysfunction in Alzheimer Disease) (to TV); VEGA Grant No. 2/0148/16 (to TH); the Torsten Söderberg Foundation (to KB); the Wallenberg Academy Fellows program, the Swedish Research Council Grant No. 2018-02532, the European Research Council Grant No. 681712 (to HZ) and the Swedish State Support for Clinical Research Grant No. ALFGBG-720931 (to HZ); the Knut and Alice Wallenberg Foundation (Wallenberg Centre for Molecular and Translational Medicine), the Swedish Research Council, the Swedish State Support for Clinical Research, and the Swedish Alzheimer Foundation (to MS).

KB has served as a consultant or at advisory boards for Alector, Alzheon, CogRx, Biogen, Lilly, Novartis, and Roche Diagnostics and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg, all unrelated to the work presented in this article. HZ has served at scientific advisory boards for Roche Diagnostics, Wave, Samumed, and CogRx and is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg (all outside submitted work). MS has served on an advisory board for Servier (outside scope of submitted manuscript). TV, MN, TS, TH, and NZ are affiliated with AXON Neuroscience SE, which develops tau-based immunotherapy. AL, CC, and NJA report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received May 28, 2019; revised Sep 20, 2019; accepted Sep 24, 2019.

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