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Tau-Mediated Synaptic and Neuronal Dysfunction in Neurodegenerative Disease

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Abstract

The accumulation of pathological tau in the brain is associated with neuronal deterioration and cognitive impairments in tauopathies including Alzheimer's disease. Tau, while primarily localized in axons of healthy neurons, accumulates in the soma and dendrites of neurons under pathogenic conditions. Tau is found in both presynaptic and postsynaptic compartments of neurons in Alzheimer's disease. New research supports that soluble forms of tau trigger pathophysiology in the brain by altering properties of synaptic and neuronal function at the early stages of disease progression, before neurons die. Here we review current understanding of how tau-mediated synaptic and neuronal dysfunction contributes to cognitive decline. Delineating the mechanisms by which pathogenic tau alters synapses, dendrites and axons will help lay the foundation for new strategies to restore neuronal function in tauopathy.

Introduction

The finely tuned electrochemical communication between neurons in the brain is essential for cognition and behavior. In neurodegenerative tauopathies, the ability of neurons to encode information is compromised leading to cognitive decline and behavioral impairments. Tauopathies, including Alzheimer's disease (AD), are characterized by increased levels of pathologically aggregated tau in the brain that correlate with the deterioration of synapses and neurons [1,2]. In AD, tau localization is abnormally shifted from axons into the somatodendritic compartment, a process associated with accumulation of amyloid β [3]. The mechanistic links between amyloid β (Aβ) and tau in causing synapse dysfunction have been reviewed by others recently [4,5]. Here, we will focus on tau-mediated neuronal and synapse dysfunction.

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Tau is normally enriched in the axons. The current prevailing view is that aberrant forms of mislocalized or secreted tau is toxic to neurons in disease [6]. Importantly, studies on tauopathy mouse models support that toxic tau triggers neuronal dysfunction underlying cognitive impairments without widespread neuron loss [7,8]. While the majority of tauopathy cases are sporadic, there are over fifty familial tau mutations that cause frontotemporal lobar degeneration with tau inclusions (FTLD-tau). A recent review of current strategies for the diagnosis and therapeutic intervention in tauopathies provides insight into the challenges associated with understanding these diseases [9]. Many studies that have shaped the tauopathy field were done on transgenic mice that express human tau carrying familial FTLD-tau mutations that cause frontotemporal dementia (FTD) [7,10–16]. These transgenic mouse lines exhibit different degrees of age-dependent tau pathology, pathophysiology, neuron loss, and behavioral deficits. However, there is a strong link between neuronal dysfunction and cognitive decline among the tauopathy mouse models.

The spreading of toxic tau across neuronal circuits may accelerate pathogenesis in the brain. Growing efforts to uncover the mechanisms that promote tau propagation in neurodegenerative diseases have been reviewed by others recently [17,18]. In this review, we will focus on recent advances to delineate the sequence of events triggered by tau that lead to synapse decline and neuronal dysfunction in tauopathy. We will highlight new findings about the identities of toxic forms of tau how toxic tau disrupts the function of synapses, dendrites and axons during pathogenesis (Figure 1).

Soluble tau oligomers vs. insoluble aggregates in neurons

The accumulation and spread of insoluble tau inclusions in the form of neurofibrillary tangles (NFTs) is considered a pathological hallmark of tauopathies. However, soluble forms of tau oligomers, not NFTs, have emerged a as key toxic species in causing neuronal dysfunction and cognitive decline [10,19]. Tau oligomers accumulate in the human brain in AD [20,21] and progressive supranuclear palsy [22], and increased levels of multimeric tau correlate with memory decline in human tau P301L mutant mice (rTg4510) [23]. Injection of recombinant human tau oligomers, but not human tau monomers or fibrils, into mouse brain impaired memory [24]. Passive immunization targeting soluble tau oligomers exerted protective effects in a mouse model of tauopathy [25].

At the cellular level, exogenously applied human tau oligomers triggered the aggregation and somatodendritic mislocalization of endogenous tau in cultured mouse neurons [26]. At the synapse level, tau oligomers caused internal calcium dysregulation and loss of both synapsin and synaptophysin at presynaptic terminals in human iPSC-derived neurons [27•]. In contrast to the toxicity induced by soluble tau oligomers, there is evidence that insoluble tau oligomers may be non-toxic and even protective for neuron function [28]. Indeed, it is possible that various forms of tau oligomers exist and that their toxicity may depend on oligomer solubility, stoichiometry, structure, or tau post-translational modifications (PTMs).

Familial FTLD tau mutants in synapses

Expression of human tau with FTLD mutations in mice triggers abnormal activity at anatomically distinct synaptic connections. Transgenic mice with human tau carrying P301S or P301L familial FTD-causing mutations have impaired long-term potentiation (LTP) at the Schaffer collateral-CA1 synapses in the hippocampus [7,14]. Mice expressing human tau with the familial FTD V337M mutation have reduced excitatory synaptic transmission in the ventral striatum, associated with decreased PSD-95 and synaptic glutamate receptors levels in both the ventral striatum and the insular cortex [11]. Enhancing NMDA-type glutamate receptor (NMDAR) activation in these mice restored ventral striatal neuron firing and reversed FTD-associated repetitive behaviors. In two independent lines of transgenic mice expressing human tau with the A152T FTD-associated mutation, mossy fiber-CA3 synaptic transmission was found to be elevated without alterations of LTP expression [15,16]. A152T tau or wildtype tau overexpression increased synaptic vesicle release probability in acute slices from aged mice [15], and the A152T mutation increased levels of glutamate and excitotoxicity in hippocampal slice cultures, likely via extra-synaptic mechanisms [16]. The selective vulnerability of particular synapses to tau toxicity may depend on their individual physiological properties and synaptic machinery.

More detailed analyses of FTD-causing tau mutants on presynaptic function was performed at the *Drosophila* neuromuscular junction. The expression of three human FTLD-tau mutants, R406W, V337M or P301L, increased F-actin enrichment and reduced the mobility of synaptic vesicles in presynaptic boutons [29]. More recently, they showed that tau appears to regulate vesicle release and presynaptic function through a direct interaction with a vesicular protein called Synaptogyrin-3 [30•]. Our understanding of how FTD-causing tau mutations alter presynaptic vesicle release is quickly expanding. Further investigations into the molecular mechanisms by which FTLD mutant tau affects the integrity of synaptic transmission may uncover additional tau-interacting proteins at synapses.

Tau with aberrant post-translational modifications in synapses

Tau undergoes extensive PTMs, including phosphorylation, acetylation, ubiquitination, methylation, glycosylation, and proteolytic cleavages [31]. While some of the PTMs occur under physiological conditions, aberrant PTMs on tau could play critical roles in triggering synapse dysfunction and deterioration. In cultured hippocampal neurons, expression of a tau mutant that mimics the phosphorylation of 14 residues reduced the number of AMPA-type glutamate receptors (AMPAR) at synapses [14]. In a series of studies, we identified aberrantly acetylated lysines on tau that are associated with impairments in hippocampal synaptic plasticity and memory. Mice expressing human tau with mutations to mimic the acetylation of K274 and K281 had deficits in spatial and pattern separation memory associated with obstructed LTP in the dentate gyrus [32•]. Mechanistically, the acetylated tau mimic causes the loss of postsynaptic KIBRA and impaired AMPAR trafficking during LTP. Importantly, treating a tauopathy mouse model with salsalate, a drug that reduces tau acetylation in the brain, protected against memory deficits [33]. New evidence suggests that cleaved forms of tau may also contribute to synaptotoxicity. Blocking the caspase-2 cleavage of human P301L tau by mutating the Asp314 residue on tau restored AMPAR-mediated

synaptic transmission in neurons as well as memory deficits in mice [34••]. Moreover, the caspase-3 cleavage of tau at the Asp421 residue may contribute to tau propagation and synaptotoxicity in neurons [35,36]. There are growing efforts to identify key toxic tau PTMs and strategies to reduce their formation or to neutralize their toxicity, which could lead to new therapeutic interventions.

Pathogenic tau impairs dendritic spines

The strength of synaptic transmission is tightly linked to spine structural changes [37]. The size, morphology, or density spines on dendrites can change in response to neuronal activity and experience [37–39]. A recent study provided evidence that in the early stages of AD, spine density is reduced and the retrieval of stored memory, but not the encoding of long-term memory, is impaired. Using mice to model the early stages of AD, they showed that optogenetic induction of LTP in engram-specific dentate granule cells increased dendritic spine density and restored memory deficits [40••]. This works highlights the contribution of spine loss to AD-related cognitive decline.

Consistent with the susceptibility of synaptic transmission to toxic tau, dendritic spines on excitatory neurons are particularly vulnerable in a tauopathy mouse model. Interestingly, in cortical neurons expressing human P301L mutant tau, the number of mushroom spines, considered stable and functional, was reduced. In contrast, the number of filipodia, considered unstable and nonfunctional, was increased [41]. The preservation of filopodia in the presence of toxic tau suggests that it might be possible to restore functional dendritic spines by strengthening synaptic connections on filipodia.

Pathogenic tau impairs axonal functions

Axons support the functional output of neurons. The axon initial segment (AIS) is a specialized region of the axon where action potential firing is initiated. The location and length of the AIS regulates neuronal excitability. In transgenic mice expressing human P301L tau, a shift of the AIS away from the soma was associated with the reduced excitability of CA1 neurons [42]. The AIS also acts as a structural barrier for the axonal compartment. Marked deterioration of the AIS structure was reported in an AD mouse model, which could underlie the missorting of axonal proteins to dendrites [43]. We found that expression of acetyl-mimic tau on K274 and K281 led to destabilization of cytoskeletal-associated proteins in the AIS [44], resulting in missorting of tau to the somatodendritic compartment, where tau is particularly toxic.

Axons maintain neuronal function by the anterograde and retrograde transport of cargo [45]. In *Drosophila* motor neurons, expression of the human 3 repeat (3R) tau isoform, but not the 4 repeat (4R) isoform, led to the accumulation of vesicles in axons and caused premature lethality [46], most likely by impairing axonal transport. The exact mechanism underlying this impairment is unclear. In transgenic mice expressing Aβ and human tau, a tau-mediated reduction of kinesin-1 light chain was observed in association with impaired anterograde trafficking in axons [47]. Collectively, these studies support that pathogenic tau can disrupt

the structural components and molecular machinery in axons, which serve to support the functional output of neurons.

Conclusions

Increasing evidence supports tau playing a key role setting into motion the early pathogenic events that contribute to cognitive decline in neurodegenerative disease. Recent advances reviewed herein shape our current understanding of how pathogenic tau in neurons contributes to synaptic and neuronal dysfunction. Tau-mediated neuronal decline may also involve non-neuronal cells in the brain. Recently, microglia, TREM2 and inflammation have been implicated in tau-mediated pathogenesis and the deterioration of neurons [48,49], but how microglia and inflammation in neurodegenerative disease contribute to synaptic and neuronal dysfunction is not well understood. Given that toxic tau can affect the regulation of postsynaptic strength, dendritic spine density, the AIS, axonal transport, and presynaptic vesicle release dynamics, there are multiple mechanisms by which tau can promote neuronal dysfunction. Moving forward, it will be important to dissect the tau-dependent mechanisms underlying these functional effects and explore new approaches that can restore neuronal function and cognition in tauopathy.

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Highlights

- Soluble tau oligomers promote pathophysiology in neurons
- Pathogenic tau affects mechanisms that regulate both presynaptic and postsynaptic function
- Deterioration of axons in tauopathy involves the dysregulation of the axon initial segment and impaired axonal transport
- Loss of dendritic spines underlies memory impairments in tauopathy mouse models

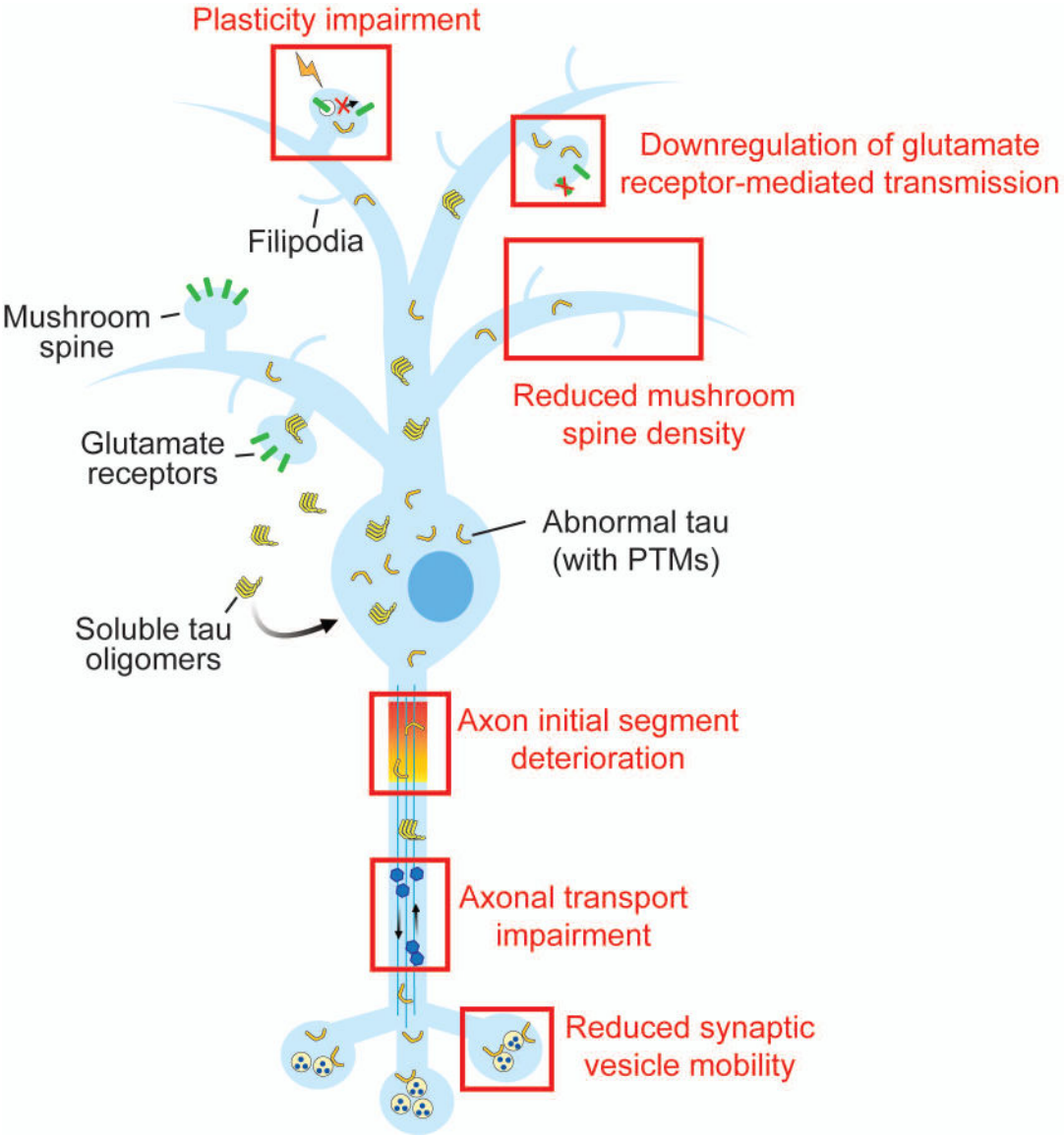

Figure 1.

Pathogenic forms of tau, including soluble tau oligomers and tau with abnormal post-translational modifications (PTMs), can promote neuronal dysfunction by multiple mechanisms at the early stages of neurodegenerative disease. At postsynaptic sites, pathogenic tau reduces glutamate receptor levels and inhibits receptor trafficking during synaptic plasticity. The tau-mediated loss of mushroom spines is associated with increased filipodia on dendrites. Axonal function is compromised by tau due to the destabilization of the axon initial segment and deficient axonal transport. At the presynaptic terminal, tau decreases the release of neurotransmitter-containing synaptic vesicles by reducing their mobility in the terminal.