Review

The intersection of amyloid beta and tau in glutamatergic synaptic dysfunction and collapse in Alzheimer's disease

Johanna L. Crimins[a], Amy Pooler[b,c], Manuela Polydoro[c], Jennifer I. Luebke[a], Tara L. Spires-Jones[c,*]

[a] Boston University School of Medicine, Boston, MA, USA
[b] King's College London, UK
[c] Massachusetts General Hospital, Harvard Medical School, 114 16th Street, Charlestown, MA 02129, USA

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ABSTRACT

The synaptic connections that form between neurons during development remain plastic and able to adapt throughout the lifespan, enabling learning and memory. However, during aging and in particular in neurodegenerative diseases, synapses become dysfunctional and degenerate, contributing to dementia. In the case of Alzheimer's disease (AD), synapse loss is the strongest pathological correlate of cognitive decline, indicating that synaptic degeneration plays a central role in dementia. Over the past decade, strong evidence has emerged that oligomeric forms of amyloid beta, the protein that accumulates in senile plaques in the AD brain, contribute to degeneration of synaptic structure and function. More recent data indicate that pathological forms of tau protein, which accumulate in neurofibrillary tangles in the AD brain, also cause synaptic dysfunction and loss. In this review, we will present the case that soluble forms of both amyloid beta and tau protein act at the synapse to cause neural network dysfunction, and further that these two pathological proteins may act in concert to cause synaptic pathology. These data may have wide-ranging implications for the targeting of soluble pathological proteins in neurodegenerative diseases to prevent or reverse cognitive decline.

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Contents

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. It is a terrible burden for patients, their families, and caregivers, and it is also a potentially crippling public health problem for the entire world due to our aging population.

The most significant risk factor for AD is age. Approximately 1 in 8 people over 65 is diagnosed with Alzheimer's and the risk of disease doubles every five years to over 40% of people over 80 diagnosed with the disease (Association, 2012). Pathologically, AD is characterized by atrophy of the hippocampus and neocortex resulting from neuron and synapse loss and the deposition of two proteinaceous lesions: senile plaques, composed primarily of the amyloid beta peptide (Aβ) and neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein (Gomez-Isla et al., 2008). Fig. 1 summarizes the pathological lesions observed in AD.

* Corresponding author. Tel.: +1 617 726 1263; fax: +1 617 724 1480.
  E-mail addresses: tspires@partners.org, sparatires@gmail.com
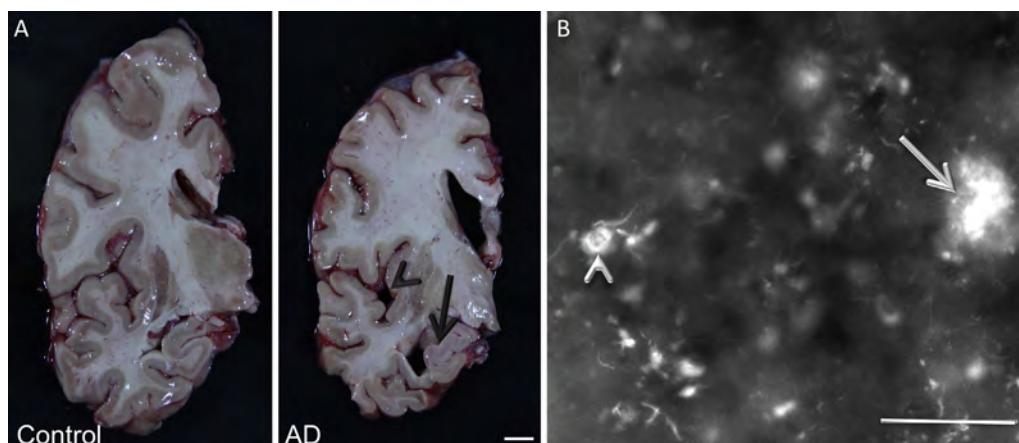(T.L. Spires-Jones).

Fig. 1. Alzheimer's disease pathology. AD patient brains are characterized by gross atrophy of the hippocampus (arrow in A) and cortical thinning (arrowhead in A). Microscopically, the disease is defined by the presence of amyloid plaques (arrow in B) and neurofibrillary tangles (arrowhead in B). Plaques and tangles are both labeled by histological amyloid binding dyes such as thioflavin S shown here in panel B. Scale bars 1 cm in A, 20 μm in B.

Of the pathological changes in the brain, the loss of synapses, the connections between neurons, is the strongest correlate of cognitive decline (DeKosky and Scheff, 1990; Terry et al., 1991). Synapse loss also exceeds the amount that would be predicted by the loss of connections from neurons that die in the brain (Arendt, 2009; Coleman and Yao, 2003). This indicates that synaptic degeneration plays a central role in causing dementia. During development, the formation and pruning of synaptic connections is highly dynamic. Furthermore, the ability of synapses to change in response to neural activity is retained throughout adulthood. A widely held view is that this synaptic plasticity plays a key role in the ability to learn and to form new memories (Bourne and Harris, 2008; Caroni et al., 2012). Loss of synapses is common to all neurodegenerative diseases. Since synapses are plastic, they have the potential to be restored, thus they are an attractive target for therapeutic intervention. As such, the cause of synapse dysfunction and loss in AD has been the focus of many studies over the past several years.

Altered Aβ production is strongly implicated in the initiation of AD by genetic mutations associated with rare familial cases and those cases associated with trisomy 21, which triplicates the precursor of Aβ (amyloid precursor protein) (Bertram and Tanzi, 2008). Because of this strong evidence linking Aβ to AD pathogenesis, much of the work on synapse degeneration has focused on Aβ, as will be summarized in Section 2. However, amyloid pathology does not correlate well with cognitive decline or synapse loss in AD, and the recent failure of Aβ-directed therapeutics (Karran et al., 2011) has prompted more research into the role of tau in synapse loss, as will be discussed in Section 3. Finally, in Section 4 we discuss interesting new data that implicate tau in Aβ-mediated synapse degeneration, providing a link between the initiating factor in AD, Aβ, and the tau pathology, which correlates better with synapse loss and dementia in the disease.

2. Oligomeric amyloid beta contributes to synapse dysfunction and loss in Alzheimer's disease

The protein aggregates observed in the AD brain – plaques and tangles – were described over a century ago by Alois Alzheimer when he examined the brain of a patient with dementia, and these lesions are still the defining features of the disease (Alzheimer, 1907; Goedert and Spillantini, 2006). Over the past 30 years, the molecular nature of these aggregates has been elucidated. Amyloid plaques are extracellular deposits of Aβ (Glenner and Wong, 1984; Masters et al., 1985), which is produced by sequential cleavage

of the amyloid precursor protein by beta and gamma secretases (Kang et al., 1987; Selkoe, 2001). Dense plaques that stain with amyloid binding dyes such as congo red and thioflavin S are associated with disruptions in the local neuropil including marked synapse loss (Gomez-Isla et al., 2008), but plaque burden in the brain does not correlate with synapse loss or with the progression of dementia (Ingelsson et al., 2004). Instead, it appears from the work of many groups that soluble forms of Aβ are toxic to synapses and detrimental to cognition. The important role of soluble, oligomeric Aβ in the degeneration of synapses has been extensively reviewed recently (Koffie et al., 2011; Selkoe, 2008; Sheng et al., 2012), so here we will summarize the most important points.

2.1. Oligomeric Aβ causes synapse dysfunction and loss in vitro and in vivo

Several types of soluble oligomeric assemblies of Aβ including oligomers of synthetic Aβ, naturally secreted Aβ from APP overexpressing cells, and Aβ oligomers isolated from human AD patient brains cause synapse loss when applied to cultured neurons, while Aβ monomers and mature fibrils are relatively inert (Lacor et al., 2004; Lambert et al., 1998; Wu et al., 2010). Oligomeric Aβ secreted from APP overexpressing cells or isolated from human AD brain also cause synaptic dysfunction in brain slices including impairment of long-term potentiation and enhancement of long-term depression (Li et al., 2009, 2011; Shankar et al., 2007, 2008; Wang et al., 2002). Transgenic animal models that express human APP with mutations that cause familial AD develop plaques and exhibit dendritic spine loss in the vicinity of plaques (Lanz et al., 2003; Moolman et al., 2004; Spires et al., 2005; Tsai et al., 2004). Animals expressing mutant human APP and presenilins also develop marked synaptic dysfunction, in many cases at ages before overt plaque deposition, indicating an important role for soluble Aβ in this process (Koffie et al., 2011; Selkoe, 2002; Spires-Jones and Knafo, 2012). When injected into the brains of rodents, oligomeric Aβ causes behavioral impairments, spine loss, and impaired LTP, indicating that the soluble oligomeric forms of Aβ rather than plaques themselves are responsible for synaptic degeneration (Cleary et al., 2005; Shankar et al., 2008; Walsh et al., 2002).

A recent advance in imaging synapses called array tomography allows for direct visualization of the protein composition of individual synapses in postmortem brain tissue (Micheva et al., 2010; Micheva and Smith, 2007). Using this technique, oligomeric Aβ (labeled with the conformation-specific NAB61 antibody) has been observed at individual dendritic spines where it correlates

with spine shrinkage and loss (Koffie et al., 2009). This technique can also be applied to human brain tissue, where it has been confirmed that oligomeric Aβ is present at a subset of synapses where it contributes to synaptic shrinkage and loss (Koffie et al., 2012).

Several potential molecular mechanisms have been suggested to underlie the detrimental synaptic effects of oligomeric Aβ. First, glutamatergic neurotransmitter receptors are known to be affected by oligomeric Aβ. NMDA receptors are required for the observed oligomeric Aβ-induced reductions in LTP (Roselli et al., 2005; Shankar et al., 2007), and oligomeric Aβ is also known to enhance LTD by causing internalization of AMPA receptors and NMDA receptors (Hsieh et al., 2006; Snyder et al., 2005). These effects on synaptic glutamate receptors are thought to be mediated at least in part by an increase in intracellular calcium, which then activates calcineurin (Kuchibhotla et al., 2008; Rozkalne et al., 2011; Wu et al., 2010). Changes in synaptic mitochondria including altered mitochondrial dynamics, transport, and function have been noted in association with synaptic dysfunction and loss in APP over-expressing models (Balietti et al., 2013; Leuner et al., 2012), which could also be associated with the aforementioned calcium changes as mitochondria are essential in calcium buffering. Non-apoptotic caspase activation is also induced by oligomeric Aβ, which could contribute to enhanced LTD and synapse loss (D'Amelio et al., 2011). S-nitrosylation of the kinase Cdk5 has also been shown to contribute to Aβ mediated synapse loss (Qu et al., 2011). Interestingly, several of these mechanisms, calcium dysregulation, altered synaptic mitochondria, kinase regulation, and caspase activation, are all physiologically interrelated and may also be modified by tau as will be discussed in Section 4, indicating that the synaptic effects of Aβ are dependent upon tau through these pathways.

3. An emerging role for tau in synaptic dysfunction and loss

In contrast to the wealth of data implicating oligomeric Aβ in synapse degeneration, much less was known about the role of tau in synaptic dysfunction and loss until very recently. The association of NFT with synapse and neuronal loss led to the assumption that tangles themselves are toxic, but recent data have shown that, similar to oligomeric Aβ, it is the soluble forms of tau, not the tangles that are the species most toxic to synapses (Crimins et al., 2011, 2012; Kopeikina et al., 2012a; Rocher et al., 2010).

3.1. Soluble tau causes synaptic dysfunction and loss

Disruptions in the level of synaptic proteins and retraction of dendritic spines have been demonstrated in a number of models of tauopathy. Several studies proposed that aggregated tau may cause synaptic damage (Eckermann et al., 2007; Hall et al., 2001; Katsuse et al., 2006), however, there is increasing evidence to suggest that soluble tau species are the principal toxic entity underlying synapse loss in neurodegenerative tauopathies. In support of the toxicity of soluble tau, synapse loss in two transgenic mouse models of tauopathy precede substantial NFT formation (Yoshiyama et al., 2007; Eckermann et al., 2007). Primary neuronal culture studies also support the role of mislocalized soluble tau in synapse loss since spine loss has been reported specifically along dendrites into which tau is missorted (Zempel and Mandelkow, 2011). In neurons cultured from the rTg4510 mouse model, early mislocalization of abnormally phosphorylated mutant (P301L) tau to dendritic spines of is associated with decreased expression of AMPA glutamate receptor subunits 1 and 2/3 (GluA1, GluS2/3) and NMDARs (Hoover et al., 2010); potentially explaining the subsequent loss of synapses observed at later ages in these mice. A study using the array tomography technique to examine synapse loss in the rTg4510 mouse model showed slightly increased synaptic densities in cortex at

5.5 months of age, before significant tangle accumulation in this region, followed by dendritic spine loss, synapse loss, and loss of synaptic proteins (PSD95, synapsin, GluA1, and NMDA receptors) in remaining synapses at a later age (8.5 months) when tangles are abundant. However, the presence of aggregated tau in dendrites did not correlate with synapse loss, again implicating soluble tau species in synapse loss in this model (Kopeikina et al., 2012b). Very strong evidence supporting the role of soluble tau in synapse loss came from a recent study showing that subcortical injection of pre-filamentous tau oligomers leads to decreased spine density in the hippocampus of wild-type mice (Lasagna-Reeves et al., 2011).

There have been many studies in the past few years on the consequences of tau pathology on excitatory synaptic responses, which reported conflicting results. These studies report decreased (Hoover et al., 2010; Polydoro et al., 2009; Yoshiyama et al., 2007), increased (Boekhoorn et al., 2006; Polydoro et al., 2009) or unchanged (Boekhoorn et al., 2006; Polydoro et al., 2009; Schindowski et al., 2006; Sydow et al., 2011) baseline glutamatergic synaptic transmission and long-term potentiation (LTP) in hippocampal neurons of several mouse models of tauopathy in various stages of disease progression. Hoover et al. (2010) suggested that removal of GluA1 AMPARs, caused by mislocalization of hyper-phosphorylated tau to spines, underlies impaired baseline synaptic transmission and LTP that they observed in the hippocampus of young rTg4510 mice and AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs) in primary hippocampal neurons cultured from rTg4510 mice (Hoover et al., 2010).

A recent series of studies correlating synaptic function and neuronal structure have provided key insights into the role of soluble tau in synaptic dysfunction and neuronal atrophy, and the ability of neurons to compensate for tau-induced pathological changes (Crimins et al., 2011, 2012; Luebke et al., 2010; Rocher et al., 2010). In these studies of frontal cortical neurons in the rTg4510 model, resting membrane potential was significantly depolarized, and the depolarizing voltage deflection or "sag" evoked by hyperpolarization was higher in amplitude compared to neurons from non-transgenic brain. Importantly, these electrophysiological changes occurred in both tangle bearing and non-tangle bearing cells, implicating soluble rather than fibrillar forms of tau as important for synaptic dysfunction (Rocher et al., 2010). Significant structural atrophy including regression of apical dendritic tufts and dendritic spine loss were also observed, and again the presence of a neurofibrillary tangle was not required for structural degeneration (Crimins et al., 2012; Rocher et al., 2010). Functional electrophysiological changes precede significant regressive structural changes to dendritic architecture and spines (Crimins et al., 2012), implying different pathogenic mechanism underlying functional and structural changes.

Another important finding to come out of these studies is that neurons in rTg4510 cortex compensate structurally and functionally for tau-induced degenerative phenotypes. Despite significant structural degeneration including spine loss and dendritic branching, length, and complexity, functional synaptic responses are not reduced in these cells, in fact surviving cells in rTg4510 cortex are more excitable than wild-type cells (Crimins et al., 2011). A sub-population of neurons in advanced stages of tauopathy in this model exhibit proliferative sprouting of oblique branches of the apical tuft. Neurons at this stage also exhibit increased numbers of filopodia (immature spines) along with loss of mature mushroom spines, indicating synaptic compensation (Crimins et al., 2012). Fig. 2 illustrates a working model of the effects of soluble tau on synaptic properties.

Downstream of synaptic dysfunction in rTg4510 mice, neural circuit function and cognition are impaired, with strong evidence that soluble tau is more disruptive than neurofibrillary tangles. The original description of this model showed Morris water maze
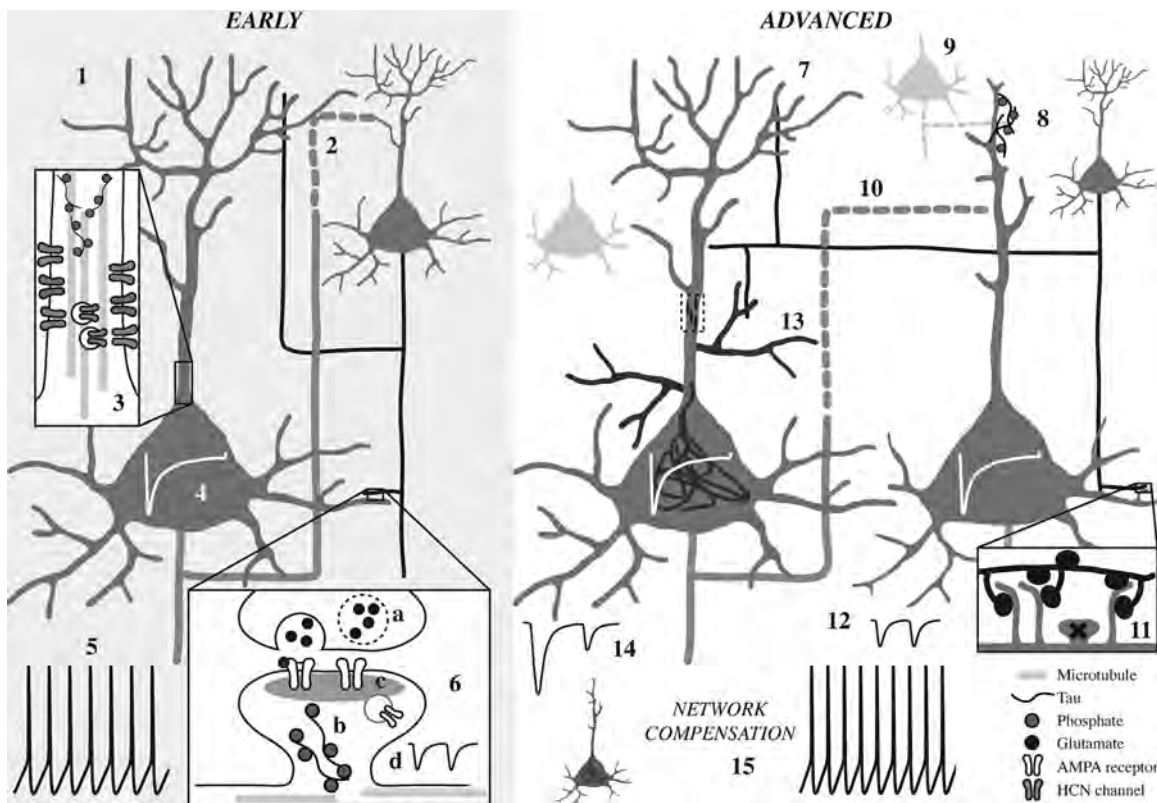
Fig. 2. Model of synaptic effects of soluble tau in the rTg4510 model of tauopathy. In early tauopathy, dendritic architecture is preserved (1). Pathological soluble tau impairs microtubule-dependent transport in axons, which begin to die back distally (2), and in dendrites, where HCN channels subsequently insert into proximal dendritic and/or somatic membranes (3). The mislocalization and high density of HCN leads to an increased amplitude depolarizing sag potential at the soma (4), which contributes to significant depolarization of the resting membrane potential and associated increased action potential firing rates (5). Impaired trafficking to presynaptic sites may lead to a reduction and/or perturbation(s) in presynaptic vesicles (6a), whereas mislocalization of pathological soluble tau to spines (6b) and global disturbances in postsynaptic targeting, anchoring and/or turnover of glutamate receptors leads to a reduced density of postsynaptic AMPA receptors (6c). Excitatory synaptic transmission is disrupted, resulting in a higher proportion of low-amplitude sEPSCs (6d). In advanced tauopathy, some neurons possess intact apical dendritic tufts (7) due to distinctive initiation and progression of tau pathology, and/or patterns of deafferentation. The apical dendritic tuft is severely atrophic or is completely lost in many neurons; trans-synaptic transmission of tau pathology may contribute to this regressive process (8). Since approximately half of frontal cortical pyramidal neurons are lost, in part due to death cascades initiated by excitotoxicity (9), and remaining axons continue to regress (10), surviving neurons are deafferented. Spines density is decreased due to a specific reduction in mushroom spines and compensatory sprouting of filopodia and axonal boutons results in the formation new, albeit smaller excitatory synapses (11); these small synapses may account for the higher proportion of low-amplitude sEPSCs exhibited by some neurons (12). Many neurons with intact apical tufts demonstrate proliferative sprouting of oblique dendrites of the apical trunk (13) and may have increased numbers of shaft synapses (dashed box); these changes are consistent with an increased mean amplitude and proportion of high-amplitude sEPSCs (14). Compensatory responses (e.g. 11 and 13), in addition to further increased action potential firing rates, allow for relatively stable network function and preservation of some frontal lobe function (15).

deficits which are reversed by transgene suppression despite the continued presence of neurofibrillary tangles (SantaCruz et al., 2005). Moreover, transcription of the immediate early gene Arc in response to environmental enrichment is impaired in rTg4510 hippocampus, and this phenotype is recovered following transgene suppression but with the continued presence of tangles (Fox et al., 2011). This study assessed on a cell-by-cell basis which neurons responded to stimulation and it was found that responses were impaired in a similar manner in both tangle-bearing cells and non-tangle bearing neurons, strongly implicating soluble tau in the impairment of neural circuit responses to physiologically relevant stimuli (Fox et al., 2011).

3.2. Potential mechanisms of tau-induced synaptic degeneration

While the mechanism of synaptic degeneration in neurodegenerative tauopathies is not yet clear, abnormal tau may impair the transport of synaptic cargoes to pre- and postsynaptic targets and therefore induce dying back of axons and subsequent neuronal loss. Since functional electrophysiological changes occur prior to substantial deposition of NFTs and neuron loss (Crimins et al., 2012)—defining features of advanced-stage tauopathy—it

is plausible that early accumulation of pathological soluble tau species (e.g. hyperphosphorylated, truncated and/or oligomeric) within the somatodendritic compartment of neurons may ultimately underlie the significantly higher sag potential amplitude and consequent hyperexcitability of rTg4510 neurons observed with electrophysiology (Crimins et al., 2011, 2012; Rocher et al., 2010). The higher sag potential amplitude is consistent with the idea that disruptions in dendritic microtubule-dependent transport of HCN channels occur early in disease pathogenesis. In support of this, a recent study showed that reduced neurite area fraction and associated perinuclear clustering of mitochondria are dependent upon the presence of high levels of pathological soluble tau species in young (5.5-month-old) rTg4510 mice (Kopeikina et al., 2011), providing strong histological evidence for early impairment of microtubule-dependent transport in this mouse model. Moreover, impaired dendritic trafficking has been proposed as a principal underlying cause for early excitatory synaptic dysfunction in response to pathological tau changes (Hoover et al., 2010) and been shown to occur in tau-transfected hippocampal neurons (Thies and Mandelkow, 2007).

How might impaired trafficking lead to a higher sag potential amplitude? HCN channels are rapidly trafficked along microtubule

and actin cytoskeletal networks in dendrites (Noam et al., 2010) and are particularly targeted to the distal dendritic arbor (Lorincz et al., 2002; Magee, 1998). Thus, early and persistent impairment of HCN channel trafficking may result in accumulation of HCN channels at the soma and/or proximal dendrites and therefore lead to high-amplitude sag potential. The progressive destruction of microtubules microtubule-dependent transport in neurodegenerative tauopathies has significant implications for the morphology of axons and dendrites. Indeed, axonal regression and dystrophy have been described in human neurodegenerative tauopathies (Ballatore et al., 2007) and in several mouse models of tauopathy (Ishihara et al., 1999; Leroy et al., 2007; Lin et al., 2003; Ludvigson et al., 2011; Probst et al., 2000; Spittaels et al., 1999). Signs of axonal and dendritic degeneration, many of which are histological correlates of axonal transport defects include: swellings containing aggregations of cytoskeletal elements and organelles such as mitochondria, substantial vacuolization, membrane folding abnormalities, and microtubule disruption. In axons, split and ballooned myelin sheaths are also observed.

Tau may directly compete with other kinesin-driven cargos (Dubey et al., 2008), impede docking of cargoes to molecular motors (Ittner et al., 2009), displace and/or reverse motor proteins (Dixit et al., 2008; Dubey et al., 2008; Stamer et al., 2002; Thies and Mandelkow, 2007), prevent access of motors to microtubules (Stamer et al., 2002; Thies and Mandelkow, 2007), or cause transport blockage by acting as a direct physical barrier or by promoting microtubule bundling (Dixit et al., 2008; Stamer et al., 2002; Thies and Mandelkow, 2007). Notably, since in healthy neurons tau binds to and promotes stabilization of microtubules primarily in the axon, these proposed mechanisms have been generated in large part from studies focusing on axonal transport deficits. While microtubule destabilization due to tau loss-of-function is one of the major mechanisms by which transport is disrupted along microtubules in axons (Ballatore et al., 2007), it is unlikely that this is exclusively the case in dendrites. It is plausible that a gain-of-function for pathological tau may contribute to microtubule destabilization leading to impaired trafficking in this compartment. Consistent with this idea, previous studies have shown that mutant tau sequesters endogenous tau and other microtubule-binding proteins, including those responsible for dendritic microtubule stabilization (Alonso et al., 1997; Iqbal et al., 2008; Sydow et al., 2011).

Pronounced regression and dystrophy of distal apical dendrites and loss of basal dendrites of hippocampal neurons have also been well documented in AD (Braak and Braak, 1997; McKee et al., 1989) and reproduced in animal models of tauopathy and these alterations may occur prior to NFT pathology. For example, adeno-associated virus (AAV)-tauP301L infection in the hippocampus of mice results in dystrophy and loss of apical dendrites of hippocampal neurons (Jaworski et al., 2011). Similarly, successive tau-mediated loss of microtubules and subsequent dendritic degeneration of first distal and then more proximal dendrites was observed in lamprey neurons (Lee et al., 2012). Loss of microtubules can occur in dendrites into which tau is missorted (Lee et al., 2012; Zempel and Mandelkow, 2011), suggesting a mechanistic link between the presence of abnormal tau species and degenerative changes to dendrites. Indeed, studies have shown that hyperphosphorylated tau sequesters endogenous tau and other microtubule-binding proteins, including those responsible for dendritic microtubule stabilization (Alonso et al., 1997; Iqbal et al., 2008; Sydow et al., 2011). There is also evidence for tau-mediated impairment of microtubule-dependent transport along dendrites (Stamer et al., 2002; Thies and Mandelkow, 2007). Therefore, as with axons, dendrites are likely deprived of proteins, vesicles and organelles that support maintenance of their structure and function.

Pathological tau may also play a role in synaptic dysfunction in a more direct fashion. In a recent study, disrupted postsynaptic targeting of Fyn kinase, which promotes interactions between NMDARs and the postsynaptic density, was observed in tau-deficient mice and in transgenic mice expressing truncated tau (Ittner et al., 2010). These data indicate that in addition to its role as a microtubule-stabilizing agent, tau plays an important role in maintaining the protein composition of the PSD in dendritic spines in healthy neurons. Thus, it is plausible that during AD pathogenesis, tau mislocalization and/or pathological modifications in tau protein may promoting alter synaptic function by directly interfering with the postsynaptic density. In support of this idea, Hoover et al. (2010) found that abnormally phosphorylated tau impairs glutamate receptor trafficking and synaptic anchoring which contributes to synaptic impairments. In human AD brain, hyperphosphorylated tau was found to be increased in biochemically isolated synaptic fractions (Tai et al., 2012), indicating that pathological tau may play a direct role in synapse loss in human disease. As will be discussed in Section 4, there are also apparently pathological interactions of tau and Aβ at the postsynaptic density.

4. The interaction of Aβ and tau at the synapse

Along with the recent important finding that tau is present in postsynaptic densities (not just bound to microtubules in axons) in healthy neurons, recent data indicate that tau may also be necessary for the well-established synaptotoxic role of oligomeric Aβ discussed in Section 2 (Ittner and Gotz, 2011). In primary cultured hippocampal neurons, application of exogenous oligomeric Aβ causes dendritic spine loss specifically in dendritic regions where there is missorting of tau to the dendrite, microtubule breakdown, and local increases in calcium concentration (Zempel et al., 2010). Oligomeric Aβ isolated from human AD brain also causes tau hyperphosphorylation associated with neuritic degeneration in cultured neurons (Jin et al., 2011). In mouse models with amyloid plaque deposition, behavioral impairments and excitotoxicity associated with Aβ were reduced on a tau null background (Roberson et al., 2007). A tau null background also improved memory function, and reduced susceptibility to excitotoxic seizures in a manner dependent on Fyn kinase localization to the postsynaptic density (Ittner et al., 2010; Roberson et al., 2011), implicating tau at dendritic spines in Aβ induced synaptic dysfunction.

These exciting data from cell culture systems and mouse models from a few groups strongly indicate that tau may be important for Aβ-mediated synaptic degeneration and lead to intriguing and testable hypotheses about whether the synapse is the link between these two pathological proteins. The synaptic effects of Aβ early in the disease process could perhaps initiate the tau pathology that is more important for neuronal loss and dementia in later phases of the disease. It is worth noting however, that the link between Aβ and tau in synapse loss has yet to be demonstrated conclusively in human brain. With the new array tomography technology, the association of tau with synapses can be explored in future studies.

5. Conclusions

The studies reviewed here indicate that both of the pathological proteins involved in AD (Aβ and tau) can independently cause synaptic dysfunction and loss in cell culture and animal models. Further, the interaction of these two proteins at the synapse may be important to synaptic dysfunction and loss and thus to cognitive decline. It is important to note that the data implicating both Aβ and tau in synaptic dysfunction and loss strongly support the view that it is the soluble forms of these proteins rather than the aggregated fibrillar plaques and tangles that are toxic to synapses. Since synapse loss and protein aggregation are common to all neurodegenerative diseases, these findings will have important implications for the development of therapeutic

strategies that target soluble forms of proteins involved in neurodegeneration.

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