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Invited review

A role for tau at the synapse in Alzheimer's disease pathogenesis

Amy M. Pooler, Wendy Noble, Diane P. Hanger*

King's College London, Institute of Psychiatry, Department of Neuroscience (PO37), De Crespigny Park, London SE5 8AF, United Kingdom

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ABSTRACT

Alzheimer's disease (AD) is characterized by brain deposition of amyloid plaques and tau neurofibrillary tangles along with steady cognitive decline. Although the mechanism by which AD pathogenesis occurs is unclear, accumulating evidence suggests that dysfunction and loss of synaptic connections may be an early event underlying disease progression. Profound synapse degeneration is observed in AD, and the density of these connections strongly correlates with cognitive ability. Initial investigations into AD-related synaptic changes focused on the toxic effects of amyloid. However, recent research suggests an emerging role for tau at the synapse. Even in the absence of tangles, mice overexpressing human tau display significant synaptic degeneration, suggesting that soluble, oligomeric tau is the synaptotoxic species. However, the localization of tau within synapses in both healthy and AD brains indicates that tau might play a role in normal synaptic function, which may be disrupted in disease. Tau is able to impact synaptic activity in several ways: studies show tau interacting directly with post-synaptic signaling complexes, regulating glutamatergic receptor content in dendritic spines, and influencing targeting and function of synaptic mitochondria. Early trials of tau-targeted immunotherapy reduce tau pathology and synapse loss, indicating that the toxic effects of tau may be reversible within a certain time frame. Understanding the role of tau in both normal and degenerating synapses is crucial for the development of therapeutic strategies designed to ameliorate synapse loss and prevent AD pathogenesis.

This article is part of the Special Issue entitled 'The Synaptic Basis of Neurodegenerative Disorders'.

1. Synapse loss in Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and profound memory loss. Brains affected by AD display widespread neuronal loss and gross atrophy of the cortex and hippocampus. AD is characterized by lesions throughout the brain that are caused by deposition of amyloid beta peptide (Aβ) to form plaques, and aggregation of highly phosphorylated tau protein to form neurofibrillary tangles (Duyckaerts et al., 2009). These pathological features continue to develop over the course of the disease (Braak and Braak, 1991); tangle formation, rather than amyloid plaque deposition, is better correlated with the cognitive decline observed in AD patients (Nelson et al., 2012). However, the closest correlate may be synapse density, since analyses of AD brains revealed that the extensive synapse loss that occurs in disease (Masliah et al., 1989) strongly correlates with cognitive impairment (DeKosky and Scheff, 1990; Terry et al., 1991; Serrano-Pozo et al., 2011). Cognitive ability in AD patients is also closely related to the density of presynaptic glutamatergic boutons (Bell et al., 2007). Synaptic decline occurs early in disease progression; neuron death is not sufficient to explain the magnitude synapse loss, suggesting that synapses are selectively removed prior to cell death (Arendt, 2009). Furthermore, analysis of AD brains reveals alterations in genes involved in synaptic vesicle trafficking in the hippocampus (Begcevic et al., 2013) and in frontal cortex (Yao et al., 2003). Since proper synaptic function is crucial for memory formation or learning (Cooper and Bear, 2012), dementia in AD may therefore be attributed to progressive reduction in synaptic integrity (Selkoe, 2002).

Much of the work related to synapse loss in AD has focused on Aβ, a peptide formed from cleavage of amyloid precursor protein (APP), mutations in which cause familial AD (Goate et al., 1991). A sizeable body of evidence has demonstrated that soluble, oligomeric Aβ can cause synaptic dysfunction and toxicity (Sheng et al., 2012; Sivanesan et al., 2013). The synaptotoxicity of oligomeric Aβ has encouraged extensive investigation of Aβ-targeted therapeutics to slow or prevent AD pathogenesis. However, treatments that reduce Aβ, for example by immunotherapy, have not yet proved successful in clinical trials, despite promising pre-clinical results (Solomon and Frenkel, 2010; Liu et al., 2012b).

* Corresponding author. Tel.: +44 (0)207 848 0041.
E-mail address: diane.hanger@kcl.ac.uk (D.P. Hanger).

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Although the synaptotoxic effects of Aβ are well established, less is known about the role of tau at the synapse (Crimins et al., 2013). Tau was thought to be primarily a microtubule-associated protein, mainly functioning to bind and stabilize microtubules in a phosphorylation-dependent manner (Mandelkow et al., 1995). Tau contains numerous phosphorylation epitopes, many of which become abnormally phosphorylated in AD (Derkinderen et al., 2005; Hanger et al., 2007). Changes in tau phosphorylation are known to induce loss of function of tau by preventing interaction with microtubules (Bramblett et al., 1993); might there be other functions of tau that are also disrupted in AD? Indeed, accumulating evidence suggests additional roles for tau (Pooler and Hanger, 2010), including regulation of synaptic function and neuronal signaling (Reynolds et al., 2008; Souter and Lee, 2010; Usardi et al., 2011). Furthermore, a growing body of work, discussed below, suggests that tau may be involved in synaptic dysfunction in dementia. For example, in AD brain, a reduction in presynaptic protein expression is strongly correlated with the presence of tangles and phosphorylated tau (Coleman and Yao, 2003). Investigating the role of tau beyond microtubule stabilization may therefore be potentially interesting for developing new therapeutic strategies for protecting synapses in dementia.

2. Tau in the synapse

Interestingly, depletion of tau in mice by knocking out the *MAPT* gene causes no overt disease phenotype (Ke et al., 2012), although muscle weakness (Ikegami et al., 2000) and decreased locomotion were observed in aged mice from one of the knockout strains (Lei et al., 2012). Indeed, loss of tau has been shown not to affect the number of dendritic spines (Tackenberg et al., 2013). However, removal of tau during development does appear to impair neuronal maturation. Knockdown of tau in developing brains, by injection of shRNA into mouse embryos, impaired radial migration of neurons to the superficial layers of the cortex (Sapir et al., 2012). Neurons lacking tau also displayed shortened axons and dendrites, smaller soma, and a reduction of approximately 60% in the size of synaptic boutons. Furthermore, cultured hippocampal neurons from tau knockout mice extend axons and dendrites at a slower rate than wild-type neurons (Dawson et al., 2001). However, these knockout models may not provide an ideal platform for studying tau function, since tau is removed from birth and compensatory changes in other proteins may occur (Ke et al., 2012). Generation of animal models in which tau reduction is targeted and reversible could provide valuable insight into tau function.

2.1. Synaptic localization of tau

Tau has long been known to be enriched in axons (Binder et al., 1985), where it binds and stabilizes microtubules in a phosphorylation-dependent manner (Drechsel et al., 1992; Buee et al., 2000). More recently, tau has been found in additional subcellular compartments, including the synapse, where it may directly influence neuronal communication. Tau has been identified in the Golgi complex (Farah et al., 2006), rough endoplasmic reticulum (Perreault et al., 2009), and the neuronal plasma membrane (Brandt et al., 1995; Pooler et al., 2012). Localization of tau at the synapse has been the focus of several recent reports that sought to determine whether tau is located in pre-synaptic, postsynaptic, or both compartments. Tau interacts directly with filamentous F actin (Fulga et al., 2007), which is localized both in presynaptic boutons and in the head and neck of dendritic spines (Dillon and Goda, 2005). A new analysis of synapses in healthy and AD brains has provided insight into the synaptic localization of tau. In this study, analysis of human brain-derived synaptoneurosomes, containing both presynaptic and postsynaptic components, revealed tau in both compartments, and also showed that the percentage of synaptoneurosomes containing tau was the same in control and AD brain (Tai et al., 2012). However, only AD synapses contained tau phosphorylated at the PHF1 epitope (serine 396/404) and, interestingly, this form of tau was found in a greater number of postsynaptic than presynaptic sites (Tai et al., 2012). In contrast, in the brains of aged mice overexpressing P301L human tau in the entorhinal cortex, PHF1-positive tau accumulated in the presynapse (Harris et al., 2012). Taken together, these studies suggest that tau may play an important role within both the pre- and postsynapse and that its synaptic distribution may change during disease.

Indeed, a number of studies suggest that distribution of tau may be altered in AD, such that tau is no longer restricted to the axon and instead accumulates in the somatodendritic compartment (Haass and Mandelkow, 2010). In rat neurons transiently transfected with human wild-type or P301L tau, tau was expressed throughout the dendritic shaft (Hoover et al., 2010). However, examination of the dendritic spines revealed that P301L tau was significantly more likely to localize to spine heads than wild-type tau (Hoover et al., 2010). Cultured rat neurons treated with oligomeric Aβ also displayed translocation of tau from the axonal compartment to dendrites with concurrent increase of tau phosphorylation at specific epitopes (Zempel et al., 2010). Furthermore, analysis of brains from mice that regulatably express P301L human tau (Tg4510 line) by array tomography also revealed tau in dendritic

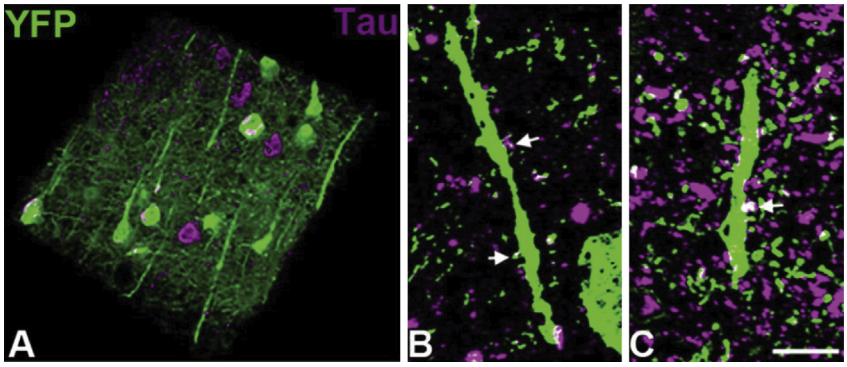

Fig. 1. In transgenic mice expressing P301L mutant human tau, the human tau is found in dendritic spines. Cortical neurons were imaged using array tomography, a high-resolution imaging technique involving immunohistochemistry on ultrathin brain sections. (A) 3D reconstruction of cortex stained for paired helical filament (PHF1) tau. Closer inspection reveals the presence of tau in a subset of dendritic spines (B) and (C), as indicated by arrows. Scale bar = 5 μm. Reproduced from Kopeikina et al. (2013).