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Dendritic Function of Tau Mediates Amyloid-β Toxicity in Alzheimer's Disease Mouse Models

Lars M. Ittner,[1,6,*] Yazi D. Ke,[1,6] Fabien Delerue,[1] Mian Bi,[1] Amadeus Gladbach,[1] Janet van Eersel,[1] Heidrun Wölfing,[1] Billy C. Chieng,[2] MacDonald J. Christie,[2] Ian A. Napier,[2] Anne Eckert,[3] Matthias Staufenbiel,[4] Edna Hardeman,[5] and Jürgen Götz[1,*]

[1]Alzheimer's and Parkinson's Disease Laboratory
[2]Neuropharmacology Laboratory
Brain and Mind Research Institute, University of Sydney, Sydney NSW 2050, Australia
[3]Neurobiology Research Laboratory, Psychiatric University Clinic, University of Basel, Basel CH-4025, Switzerland
[4]Novartis Institutes for BioMedical Research, Basel CH-4002, Switzerland
[5]Neuromuscular and Regenerative Medicine Unit, University of New South Wales, Sydney NSW 2052, Australia
[6]These authors contributed equally to this work
*Correspondence: littner@med.usyd.edu.au (L.M.I.), jgoetz@med.usyd.edu.au (J.G.)
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SUMMARY

Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) and tau deposition in brain. It has emerged that Aβ toxicity is tau dependent, although mechanistically this link remains unclear. Here, we show that tau, known as axonal protein, has a dendritic function in postsynaptic targeting of the Src kinase Fyn, a substrate of which is the NMDA receptor (NR). Missorting of tau in transgenic mice expressing truncated tau (Δtau) and absence of tau in *tau*$^{-/-}$ mice both disrupt postsynaptic targeting of Fyn. This uncouples NR-mediated excitotoxicity and hence mitigates Aβ toxicity. Δtau expression and *tau* deficiency prevent memory deficits and improve survival in Aβ-forming APP23 mice, a model of AD. These deficits are also fully rescued with a peptide that uncouples the Fyn-mediated interaction of NR and PSD-95 in vivo. Our findings suggest that this dendritic role of tau confers Aβ toxicity at the postsynapse with direct implications for pathogenesis and treatment of AD.

INTRODUCTION

Alzheimer's disease (AD) is characterized by two hallmark lesions, amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) (Ballatore et al., 2007). Aβ is derived from the amyloid-β precursor protein (APP) by proteolytic cleavage (Haass et al., 1992; Selkoe, 1997). The major constituent of NFTs is tau, a microtubule (MT)-associated protein (Goedert et al., 1988). In the course of AD, tau becomes phosphorylated, forming aggregates that deposit as NFTs and neuropil threads (Geschwind, 2003). Tau can also form aggregates in the absence of an overt Aβ pathology, for example in frontotemporal dementia (FTD), where familial mutations have been identified in the tau-encoding *MAPT* gene (Ballatore et al., 2007). Evidence that tau pathology in AD is induced by Aβ comes from our previous observation that intracerebral Aβ injections exacerbate hyperphosphorylation of tau and NFT formation in transgenic mice that express FTD mutant P301L tau (Götz et al., 2001b). A similar finding was obtained by crossing transgenic mice with NFT and plaque pathologies (Lewis et al., 2001).

Aβ-plaque formation along with memory impairment and tau pathology with increased phosphorylation, in the absence of deposition and NFT formation, has been reproduced in several transgenic mouse lines that express human APP together with pathogenic mutations identified in familial AD (Götz and Ittner, 2008; Hsiao et al., 1996; Mucke et al., 2000; Sturchler-Pierrat et al., 1997). In one of these, PDAPP, *tau* deficiency (*tau*$^{-/-}$) was shown to rescue lethality and memory deficits by an unidentified mechanism (Roberson et al., 2007).

Tau is known as axonal protein that regulates MT stability and MT-dependent processes (Dixit et al., 2008; Drechsel et al., 1992; Lee et al., 1988), while Aβ likely exerts toxicity at the postsynapse (Selkoe, 2002; Shankar et al., 2008; Zhao et al., 2006). Although in AD, hyperphosphorylated tau accumulates in the somatodendritic compartment of neurons (Ballatore et al., 2007), given the spatial separation it remains unknown how tau is involved in mediating Aβ toxicity when AD is initiated.

Seizures characterize several APP transgenic strains (Minkeviciene et al., 2009; Palop et al., 2007; Palop and Mucke, 2009) and have been associated with AD; the extent of their contribution to pathology, however, remains to be established (Minkeviciene et al., 2009; Palop et al., 2007; Palop and Mucke, 2009). Excitotoxicity results from overactivation of N-methyl-D-aspartate (NMDA) receptors (NRs). Interestingly, tau reduction decreases susceptibility to excitotoxic seizures in vivo, which may explain the concomitant improvement of the PDAPP phenotype (Roberson et al., 2007). How tau prevents excitotoxic damage at a molecular level is not understood.

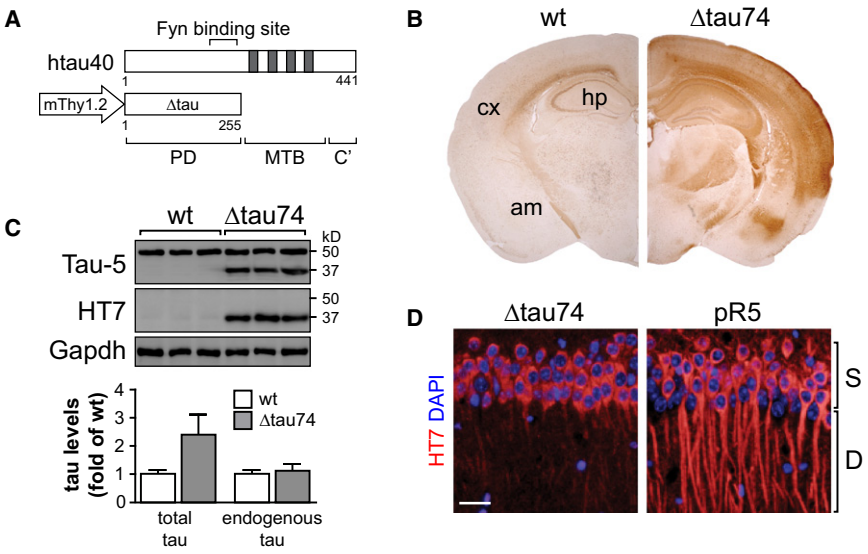

Figure 1. Truncated Tau Is Excluded from Dendrites in Δtau74 Mice

(A) The longest human tau isoform (htau40; 441 aa) is composed of an amino-terminal projection domain (PD), the microtubule-binding (MTB) domain with four repeats (gray boxes), and the carboxy-terminal tail (C′). Δtau transgenic mice express only the PD of tau under control of the neuronal mThy1.2 promoter. Δtau lacks the MTB domain and therefore the MT-binding and aggregation properties of full-length tau, but contains a Fyn binding site.

(B) Expression pattern of Δtau in Δtau74 brains. Immunohistochemistry (IHC) with a human tau-specific antibody (HT7; brown) reveals Δtau expression within several brain regions, including hippocampus (hp), cortex (cx), and amygdala (am).

(C) Western blotting of wild-type and Δtau74 hippocampal extracts reveals endogenous murine tau (50 kD) in all and Δtau (37 kD) only in transgenic samples. Quantification shows comparable levels of endogenous tau, while endogenous tau and Δtau levels add up to 2.4-fold increased total levels in Δtau74 compared to WT mice.

(D) IHC of the hippocampal CA1 region reveals that in Δtau74 mice, Δtau localizes to the soma (*S*) but is excluded from dendrites (*D*), whereas expression of P301L mutant full-length tau in pR5 mice results in a somato-dendritic localization of transgenic tau (HT7; reactive with Δtau and pR5 tau, but not endogenous tau, in red). The scale bar represents 50 μm.

Error bars represent the standard error. See also Figure S1.

Tau interacts via its amino-terminal projection domain (PD) with the kinase Fyn (Figure 1A) (Lee et al., 1998). Fyn phosphorylates the NR subunit 2 (NR2) to facilitate interaction of the NR complex with the postsynaptic density protein 95 (PSD-95) (Nakazawa et al., 2001; Rong et al., 2001; Tezuka et al., 1999), linking NRs to synaptic excitotoxic downstream signaling (Salter and Kalia, 2004). Disruption of the NR/PSD-95 interaction prevents excitotoxic damage in cultured neurons and a rat model of stroke, without affecting synaptic NMDA currents (Aarts et al., 2002). Reduction of Fyn in APP transgenic mice prevents Aβ toxicity, while overexpression enhances it (Chin et al., 2005; Chin et al., 2004).

To address how tau confers Aβ toxicity, we generated transgenic mice (Δtau74) that express only the amino-terminal projection domain (PD) of tau and crossed them with Aβ-forming APP23 and *tau*$^{-/-}$ mice. We found that tau has an important dendritic function, as in Δtau74 and *tau*$^{-/-}$ mice, postsynaptic Fyn localization is reduced, resulting in reduced NR phosphorylation, destabilized NR/PSD-95 interaction, and protection from excitotoxicity.

RESULTS

Truncated Tau Is Excluded from Dendrites

Tau comprises an amino-terminal projection domain, an MT binding (MTB) domain that mediates interaction with MTs (Butner and Kirschner, 1991; Lee et al., 1988) and is essential for tau aggregation (Crowther et al., 1989; Ksiezak-Reding and Yen, 1991) and a carboxy-terminal tail region (Figure 1A). We generated truncated (Δtau) transgenic mice that express the projection domain of tau in neurons, intended to compete with functions of endogenous tau. Four phenotypically normal lines expressed Δtau throughout the brain (Figure 1B) at comparable levels, with line Δtau74 expressing the transgene at 1.4-fold higher levels than endogenous tau (Figure 1C). Expression of Δtau neither affected levels nor distribution of endogenous tau (Figure 1C and Figures S1A–S1C available online). Consistent with previous in vitro findings (Maas et al., 2000), Δtau localized to the cell membrane, as indicated by coimmunostaining with cadherin and subcellular fractionation of membranes (Figures S1D and S1E). In AD and also full-length P301L mutant tau transgenic pR5 mice, tau is hyperphosphorylated and redistributed into the somatodendritic compartment (Figure 1D) (Götz et al., 2001a). In contrast to full-length tau, Δtau, while in the soma, was virtually excluded from dendrites (Figure 1D). In pR5 mice, tau becomes progressively hyperphosphorylated and insoluble, and eventually the mice develop NFTs. Surprisingly, Δtau in Δtau74 mice is hardly phosphorylated at all (Figure S1F).

Postsynaptic Targeting of Fyn Is Tau Dependent

Different from full-length human tau in pR5 mice, in the absence of an MTB domain, Δtau fails to interact with MTs, as determined by MT precipitation from hippocampi (Figure 2A). However, Δtau contains motifs that mediate interaction with the Src kinase Fyn, as shown in vitro (Lee et al., 1998). Accordingly, Fyn can be coimmunoprecipitated with Δtau from Δtau74 hippocampi in vivo, using a human tau-specific antibody (HT7) (Figure 2B). Immunoprecipitation (IP) with tau-specific antibodies to epitopes not present on the Δtau construct reveals a significantly reduced interaction of Fyn with endogenous tau (Figure 2B). Likewise, IP with Fyn antibodies shows a reduced interaction with endogenous tau in Δtau74 mice (Figure 2B). Together, this suggests a dominant negative effect of Δtau on the normal interaction of Fyn and endogenous tau. A similar effect on the Fyn/Tau