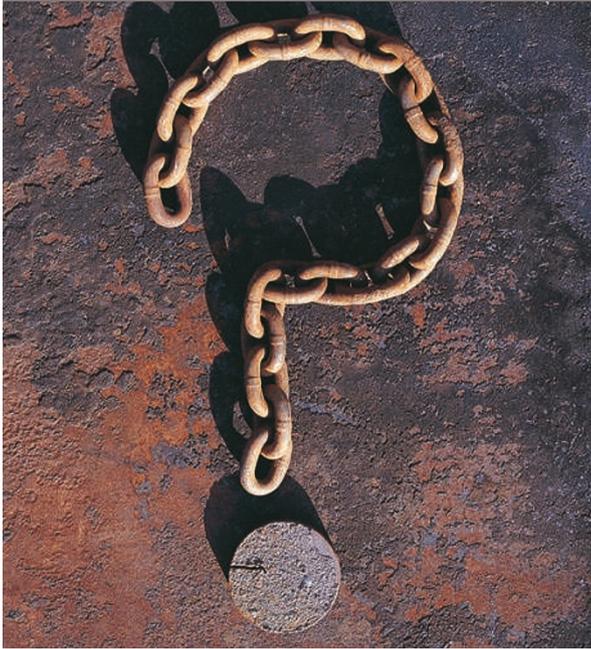


NEURODEGENERATIVE DISEASE

The missing link



Neurofibrillary tangles and amyloid plaques, which are caused by hyperphosphorylated tau and aggregation of amyloid- β , respectively, are characteristics of Alzheimer's disease. Although it has long been suggested that tau mediates amyloid- β toxicity, evidence for a direct mechanistic link has been elusive. Now, Ittner *et al.* show that tau regulates the interaction of postsynaptic density protein 95 (PSD95) with NMDARs (*N*-methyl-D-aspartate receptors), which are thought to mediate amyloid- β toxicity.

The authors generated transgenic mice that expressed the amino-terminal domain of tau (Δ tau) on

a genetically normal background of endogenous full-length tau. In contrast to the full-length tau that is hyperphosphorylated in Alzheimer's disease, Δ tau did not interact with microtubules (owing to the lack of the microtubule-binding domain), was excluded from dendrites and was hardly phosphorylated.

Previous studies have shown that the sarcoma (Src) kinase *FYN* regulates the anchoring of NMDARs in the postsynaptic density through interaction with PSD95. As Δ tau contains a binding site for *FYN* the authors performed immunoprecipitation studies and found that the interaction between *FYN* and endogenous full-length tau is significantly reduced in Δ tau mice, potentially due to competition for *FYN* binding of full-length tau and Δ tau. Furthermore, *FYN* levels in the dendrites of Δ tau-expressing neurons were greatly reduced and *FYN* accumulated in the soma, suggesting that postsynaptic targeting of *FYN* is tau-dependent. Moreover, co-immunoprecipitation experiments from brain extracts of Δ tau mice as well as tau^{-/-} mice showed that the interaction of the NMDAR subunit NR2B with PSD95 was weaker than that from extracts of wild-type mice with normal tau levels, but that this did not affect expression levels of NMDAR subunits or excitatory postsynaptic currents. These results suggest that tau is an important regulator of *FYN*-mediated NMDAR anchoring at the PSD.

To test whether destabilization of the interaction between NMDARs and PSD95 in Δ tau and tau^{-/-} mice affects Alzheimer's disease progression, the

authors crossed APP23 mice — a model for Alzheimer's disease with early onset of neuronal loss, memory deficits and premature mortality — with Δ tau or tau^{-/-} mice. In both mouse strains memory and survival improved to wild-type levels but the number of plaques and amyloid- β levels were not affected.

To test the effect of destabilizing the interaction between NMDARs and PSD95 on cell survival, the authors pretreated cultured neurons with the peptide Tat-NR2B9c, which had previously been shown to perturb the NMDAR-PSD95 interaction. Pretreatment with Tat-NR2B9c significantly reduced cell death after NMDA and/or amyloid- β treatment, which are known to signal through NMDARs and confer excitotoxicity. Encouraged by these results, the authors tested the effect of Tat-NR2B9c *in vivo* by delivering Tat-NR2B9c intracerebroventricularly in APP23 mice. Tat-NR2B9c-treated mice had an increased survival rate and performed better in a T-maze memory test than controls.

This study demonstrates that perturbing the interaction between NMDAR and PSD95 is sufficient to prevent premature death and to improve memory performance in APP23 mice. Future experiments will reveal whether these findings can be exploited for treatment of patients with Alzheimer's disease.

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ORIGINAL RESEARCH PAPER Ittner, L. M. *et al.* Dendritic function of tau mediates amyloid- β toxicity in Alzheimer's disease mouse models. *Cell* **142**, 387–397 (2010)