

Tau Reduction Prevents A β -Induced Defects in Axonal Transport

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Amyloid- β (A β) peptides, derived from the amyloid precursor protein (APP), and the microtubule-associated protein tau are key pathogenic factors in Alzheimer's disease (AD). However, the exact mechanisms by which they impair cognitive functions are unknown. Human APP (hAPP) transgenic mice have high A β concentrations in the brain and develop aberrant neuronal activity and behavioral deficits (1, 2). Lowering endogenous tau prevents these abnormalities without affecting baseline neuronal functions (1, 2). The mechanisms of this rescue are unknown. Axonal transport is critical for neuronal function and is impaired by A β (3–6). Whether tau also affects axonal transport is controversial (7–9).

To explore whether tau reduction prevents A β -induced defects in axonal transport, we studied axonal transport of mitochondria and the neurotrophin receptor TrkA, whose neuronal distributions are altered in AD (10, 11). Hippocampal neuronal cultures from tau-deficient (*Tau*^{-/-} or *Tau*^{+/-}) mice (1) and wild-type (*Tau*^{+/+}) controls were transfected with plasmids expressing fluorescent markers of mitochondria [mito-red fluorescent protein (RFP)] or TrkA (TrkA-mCherry). At 10 to 14 days in vitro, cargo motility (moving cargoes/total cargoes) and velocity ($\mu\text{m/s}$) were assessed before and after treatment with A β ₁₋₄₂ oligomers (2 μM) (12). A β rapidly inhibited axonal motility of mitochondria and TrkA in wild-type neurons. The effect was stronger on anterograde (mitochondria, $P < 0.001$; TrkA, $P < 0.001$) than retrograde (mitochondria, $P < 0.01$; TrkA, nonsignificant) transport. Complete or partial tau reduction prevented these defects without affecting axonal transport at baseline (Fig. 1 and movies S1 to S6). Moving cargoes had similar velocities in all *Tau* genotypes at baseline and after A β treatment.

Tau reduction did not enhance axonal transport under physiological conditions. However, tau levels were more critical for axonal transport in the presence of A β . A β oligomers impair axonal motility of cargoes through complex mechanisms involving *N*-methyl-D-aspartate receptor signaling (3), activation of glycogen synthase kinase 3 β (3, 4) and casein kinase 2 (5), and actin polymerization (6). Why A β requires tau to impair axonal transport is uncertain; tau might interact directly or indirectly with any of these pathways or enhance the effects independently by competing with motor proteins for microtubule access (7). Although most concentrated in axons, tau may have A β -enabling activities also in dendrites (2).

Tau ablation induces axonal spheroids in Tg2576 APP transgenic mice (13), but the functional im-

portance is unknown. Tau reduction prevents A β -induced neuronal and behavioral deficits in hAPPJ20 mice (1) and APP23 mice (2). Protection against A β -induced defects in axonal transport is one of several possible mechanisms for this rescue.

Although tau did not affect axonal transport under baseline untreated conditions in vitro (this study) or in vivo (9), it may still be important under physiologic conditions. For example, local tau gradients may promote cargo detachment at strategic points (7, 13). Tau may also regulate cel-

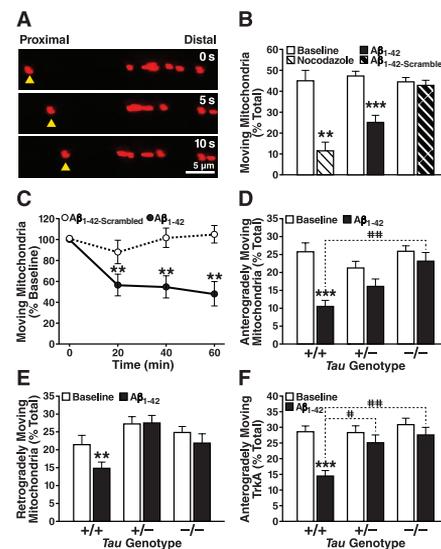


Fig. 1. (A) Anterograde axonal movement of a single mitochondrion (yellow triangles) is shown in successive 5-s image frames. (B) The microtubule-depolymerizing agent nocodazole (10 $\mu\text{g/ml}$) and oligomeric A β ₁₋₄₂ (2 μM) inhibited mitochondrial movements in *Tau*^{+/+} axons within 60 min. A β with a scrambled amino acid sequence (A β _{1-42-Scrambled}, 2 μM) had no effect. $n = 7$ to 24 axons per condition. ** $P < 0.01$, *** $P < 0.001$ versus corresponding baseline (paired t tests with Bonferroni correction). (C) A β ₁₋₄₂ inhibited mitochondrial movements in *Tau*^{+/+} axons within 20 min. $n = 7$ to 8 axons for each data point. ** $P < 0.01$ versus corresponding baseline (paired t tests, Bonferroni). (D to F) A β ₁₋₄₂ inhibited mitochondrial (D) and (E) and TrkA (F) motility in *Tau*^{+/+} axons within 60 min but not in *Tau*^{+/-} or *Tau*^{-/-} axons. $n = 24$ to 45 axons for each genotype and condition. ** $P < 0.01$, *** $P < 0.001$ versus corresponding baseline (paired t tests, Bonferroni). The percent reduction in anterograde transport in the presence of A β was greater in *Tau*^{+/+} axons than in *Tau*^{+/-} or *Tau*^{-/-} axons (D) and (F). # $P < 0.05$, ## $P < 0.01$ (Kruskal-Wallis analysis of variance, Dunn). Error bars are SEM. See also table S1.

ular transport of its binding partners (2), and tau reduction might have affected axonal transport of cargoes we did not assess. Partial tau reduction may strike a balance between therapeutic safety and efficacy because it prevented A β -induced axonal transport defects as well as aberrant neuronal activity (1), cognitive deficits (1), and premature mortality (1, 2) in hAPP mice. In addition to tau reduction strategies, components of the axonal transport machinery and of A β - or tau-related signaling cascades are potential therapeutic targets warranting further investigation.

References and Notes

- E. D. Roberson *et al.*, *Science* **316**, 750 (2007).
- L. M. Ittner *et al.*, *Cell* **142**, 387 (2010).
- H. Decker, K. Y. Lo, S. M. Unger, S. T. Ferreira, M. A. Silverman, *J. Neurosci.* **30**, 9166 (2010).
- Y. Rui, P. Tiwari, Z. Xie, J. Q. Zheng, *J. Neurosci.* **26**, 10480 (2006).
- G. Pigino *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 5907 (2009).
- H. Hiruma, T. Katakura, S. Takahashi, T. Ichikawa, T. Kawakami, *J. Neurosci.* **23**, 8967 (2003).
- R. Dixit, J. L. Ross, Y. E. Goldman, E. L. F. Holzbaur, *Science* **319**, 1086 (2008); published online 17 January 2008 (10.1126/science.1152993).
- A. Ebner *et al.*, *J. Cell Biol.* **143**, 777 (1998).
- A. Yuan, A. Kumar, C. Peterhoff, K. Duff, R.-A. Nixon, *J. Neurosci.* **28**, 1682 (2008).
- K. Hirai *et al.*, *J. Neurosci.* **21**, 3017 (2001).
- K. Schindowski, K. Belarbi, L. Bué, *Genes Brain Behav.* **7** (suppl. 1), 43 (2008).
- Materials and methods are available as supporting material on Science Online.
- H. N. Dawson *et al.*, *Neuroscience* **169**, 516 (2010).
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Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1194653/DC1
Materials and Methods
Table S1
Movies S1 to S6

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Abstract

Amyloid- β ($A\beta$) peptides, derived from the amyloid precursor protein, and the microtubule-associated protein tau are key pathogenic factors in Alzheimer's disease (AD). How exactly they impair cognitive functions is unknown. We assessed the effects of $A\beta$ and tau on axonal transport of mitochondria and the neurotrophin receptor TrkA, cargoes that are critical for neuronal function and survival and whose distributions are altered in AD. $A\beta$ oligomers rapidly inhibited axonal transport of these cargoes in wild-type neurons. Lowering tau levels prevented these defects without affecting baseline axonal transport. Thus, $A\beta$ requires tau to impair axonal transport, and tau reduction protects against $A\beta$ -induced axonal transport defects.

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