Tau-dependent microtubule disassembly initiated by prefibrillar β-amyloid

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Alzheimer's Disease (AD) is defined histopathologically by extracellular β-amyloid (Aβ) fibrils plus intraneuronal tau filaments. Studies of transgenic mice and cultured cells indicate that AD is caused by a pathological cascade in which Aβ lies upstream of tau, but the steps that connect Aβ to tau have remained undefined. We demonstrate that tau confers acute hypersensitivity of microtubules to prefibrillar, extracellular Aβ in nonneuronal cells that express transfected tau and in cultured neurons that express endogenous tau. Prefibrillar Aβ42 was active at submicromolar concentrations, severalfold below those required for equivalent effects of prefibrillar Aβ40, and microtubules were insensitive to fibrillar Aβ. The active region of tau was localized to an N-terminal domain that does not bind microtubules and is not part of the region of tau that assembles into filaments. These results suggest that a seminal cell biological event in AD pathogenesis is acute, tau-dependent loss of microtubule integrity caused by exposure of neurons to readily diffusible Aβ.

Introduction

Insoluble deposits of β-amyloid (Aβ), in the form of senile plaques, and of tau, as neurofibrillary tangles, have long been accepted as the primary histopathological markers of Alzheimer's disease (AD). Although initial research focused on the role of Aβ and tau individually, recent evidence, including data demonstrating that amyloid pathology can up-regulate tau pathology (Gotz et al., 2001; Lewis et al., 2001), defines a signaling pathway that leads from Aβ through tau (Lee et al., 2001; Selkoe, 2001; Hardy and Selkoe, 2002). Regrettably, the key steps within this pathway remain poorly understood.

A promising new focus of investigation has been the role that nonfibrillar forms of Aβ, and to a lesser extent tau, play in AD. Soluble forms of Aβ are more potent than fibrillar forms at eliciting cellular responses, such as increased apoptosis (Sponne et al., 2003) and decreased synaptic plasticity (Walsh et al., 2002). In fact, studies of transgenic animal models and AD patients have shown that cognitive deficits and synaptic loss correlate with soluble Aβ, rather than senile plaques (Kayed et al., 2003; Oddo et al., 2006), suggesting that AD is initiated well before extracellular Aβ deposits are evident.

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Abbreviations used in this paper: Aβ, β-amyloid; AD, Alzheimer's disease.

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Neuronal microtubules serve as highways for axonal transport and, by extension, are critically involved in supporting synaptic integrity and neuronal viability. The loss of axonal microtubules is a hallmark of AD, and a longstanding question has been whether their loss or the accumulation of insoluble tau filaments and Aβ plaques causes neurodegeneration. To shed light on this issue, we have used cultured neuronal and nonneuronal cells to model effects of various forms of Aβ on microtubules. Remarkably, we found that brief exposure of cells to submicromolar levels of prefibrillar Aβ42 caused massive and rapid tau-dependent disassembly of microtubules. Similar results were obtained for prefibrillar Aβ40, albeit at much higher concentrations, but microtubules in either tau-expressing or -deficient cells were relatively resistant to fibrillar Aβ. Collectively, these results highlight the most dramatic, rapid, and sensitive link between Aβ and tau described to date, identify microtubules as primary, tau-dependent targets of Aβ, and suggest that nonfibrillar Aβ and tau underlie the detrimental neurodegeneration observed in AD before the accumulation of fibrillar forms in senile plaques and neurofibrillary tangles.

Results and discussion

Coexpression of tau-CFP and YFP-tubulin in CV-1 African green monkey kidney cells, which do not express endogenous tau, allowed effects of various forms of Aβ on tau and tubulin

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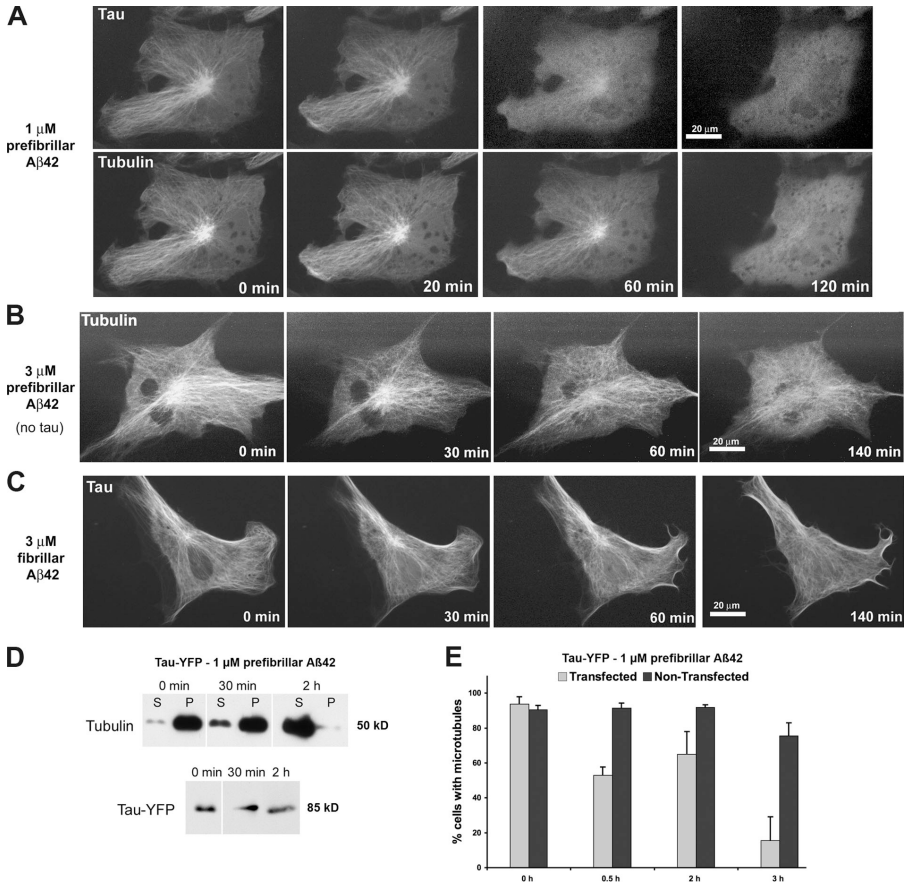

Figure 1. **Tau-dependent hypersensitivity of CV-1 cell microtubules to prefibrillar Aβ42.** CV-1 cells transfected with tau-CFP and YFP-tubulin were treated with prefibrillar Aβ42 as indicated and imaged by time-lapse fluorescence microscopy or analyzed by a biochemical assay for unassembled and polymerized tubulin (Black et al., 1996). (A) 1 μM prefibrillar Aβ42 caused tau to dissociate from microtubules and the microtubules to disassemble soon thereafter. (B) This effect required tau expression, because microtubules remained intact in cells that expressed only YFP-tubulin and were treated with 3 μM prefibrillar Aβ42. (C) Microtubules were unaffected in tau-expressing cells exposed to 3 μM fibrillar Aβ42. (D and E) Time-dependent microtubule loss induced by prefibrillar Aβ42 documented in D by fractionation of tubulin into soluble (S) and polymerized (P) pools (Black et al., 1996), and quantitation of fluorescence micrographs of fixed cells expressing Tau-CFP and counterstained with anti–α-tubulin (E). Error bars indicate the SD, and transfected and nontransfected refer to cells that did and did not express Tau-CFP, respectively.

distributions to be monitored in live cells by time-lapse fluorescence microscopy. Aβ is known to transition gradually from monomers to oligomers, protofibrils, and finally to highly stable fibrils (Bitan et al., 2003). Because we did not observe any consistent differences in behavior between freshly solubilized Aβ42, which is predominantly monomeric, versus Aβ42 enriched in octamers and larger oligomers that are recognized by a specific antibody (Kayed et al., 2003), we refer to these forms of Aβ42 collectively as "prefibrillar." It must be noted, however, that oligomers were readily detectable in freshly solubilized Aβ42 (Fig. S1, available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1). Within 30 min to 3 h after adding 0.1–3 μM prefibrillar Aβ42 to culture media, tau dissociated from microtubules, which completely disassembled soon thereafter (Fig. 1 A and Video 1). Prefibrillar Aβ40 was also capable of inducing tau-dependent microtubule disassembly in CV-1 cells, but at a minimum concentration of 3 μM (Video 2). In contrast, microtubules remained intact for >3 h when CV-1 cells expressing YFP-tubulin, but not tau-CFP, were exposed to as much as 3 μM prefibrillar Aβ42 (Fig. 1 B and Video 3). Similarly, microtubule integrity was unaffected in cells expressing tau-CFP after >2 h of exposure to as much as 3 μM fibrillar Aβ42 (Fig. 1 C and Video 4). Microtubule stability before and after exposure of cells to prefibrillar Aβ42 was also assessed using a biochemical assay that partitions unassembled and polymerized tubulin into Triton X-100–soluble and –insoluble fractions, respectively (Black et al., 1996). Prefibrillar Aβ42 led to a dramatic redistribution of tubulin into the unassembled fraction within 2 h of treatment (Fig. 1 D). This result was reinforced by quantitation of micrographs depicting Aβ42-induced microtubule loss in cells that did or did not express tau-CFP (Fig. 1 E). We thus conclude that tau makes CV-1 cell microtubules hypersensitive to prefibrillar Aβ peptides, particularly Aβ42, but not to fibrillar Aβ42.

Microtubule disassembly was also observed in primary rat cortical neurons after exposure to prefibrillar Aβ42. Discrimination between polymerized and disassembled tubulin was not evident from immunostaining of the treated neurons. Nevertheless, the immunofluorescence images show that before prefibrillar Aβ42 addition, the cells displayed numerous neuritic projections (Fig. 2 A). After only 30 min of cellular exposure to 1 μM prefibrillar Aβ42, the neurites displayed swollen varicosities, and at later time points the cells appeared to lose the majority of their neuritic projections. Similar cultures were examined by electron microscopy (Fig. 2 B). Neurites in control cells typically contained densely packed microtubules arranged in parallel. In contrast, neurites in cells treated with prefibrillar Aβ42 contained fewer, less organized microtubules and conspicuous swellings that were filled with membrane-bound organelles and were virtually devoid of microtubules. Similar findings have been reported for primary cortical neurons exposed to 5 μM oligomeric Aβ40 for 3–6 h (Sponne et al., 2003; Fifre et al., 2006).

The biochemical assay for unassembled and polymerized tubulin (Black et al., 1996) was used to monitor the effects of

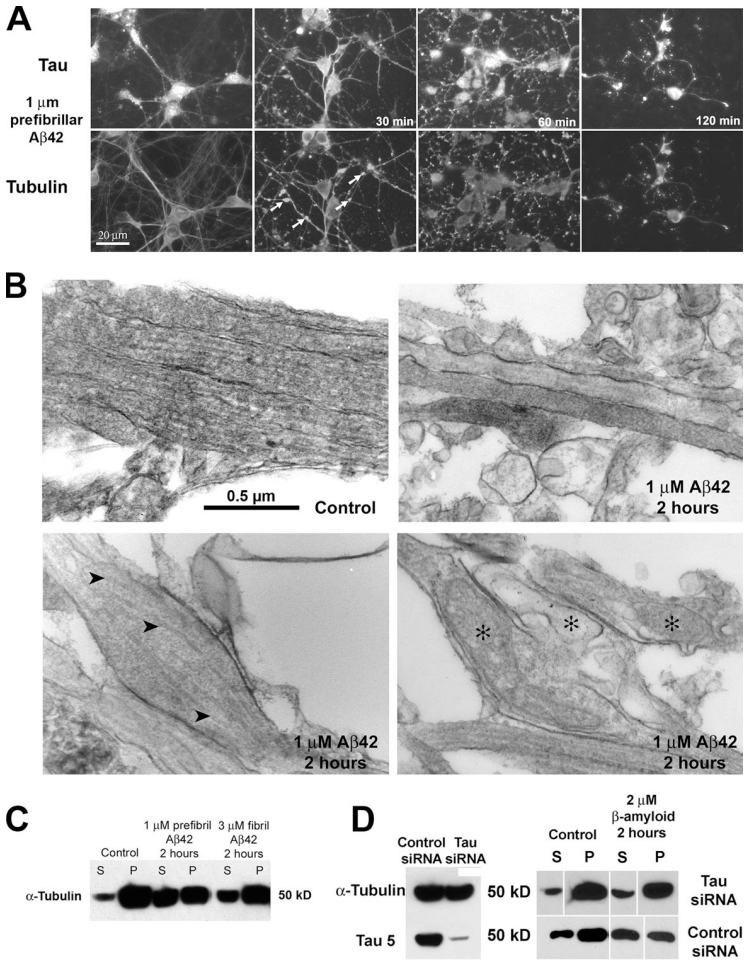

Figure 2. **Tau-dependent hypersensitivity of neuronal microtubules to prefibrillar Aβ42.** Primary rat cortical neurons were cultured for at least 8 d before treatment with prefibrillar Aβ42. (A) Cells were stained by immunofluorescence for tubulin (DM1A) and tau (R1tau) at the time points indicated after the addition of 1 μM prefibrillar Aβ42. Note the swollen varicosities induced by the Aβ42 (arrows). (B) Neurites in neurons treated for 2 h with 1 μM prefibrillar Aβ42 were found by electron microscopy to contain numerous varicosities that were filled with membrane-bound organelles (asterisks) and lacked microtubules, and additional regions with sparse, poorly organized microtubules (arrowheads). (C) Primary hippocampal neurons were extracted with Triton X-100 to separate the soluble (S) from polymerized (P) tubulin (Black et al., 1996). Note that ~90% of the tubulin was polymerized in control cultures, that only ~45% was polymerized after 2 h of cellular exposure to 1 μM prefibrillar Aβ42, and that only a modest loss of polymerized tubulin (65% polymerized) was caused by a 2-h exposure to 3 μM fibrillar Aβ42. (D) Primary neurons were transfected with a tau-specific siRNA and treated with 2 μM prefibrillar Aβ42 for 2 h before extraction. The siRNA-treated cells expressed between 1/16 and 1/32 the normal level of tau (see Fig. S1, available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1) and showed no change in tubulin levels in response to the Aβ42 treatment when compared with the tau-expressing cells.

prefibrillar and fibrillar Aβ42 on microtubule integrity in cultured hippocampal neurons (Fig. 2 C). About 90% of the tubulin was polymerized in cells that were not exposed to Aβ42, but only 45% of the tubulin was polymerized after 2 h of exposure to 1 μM prefibrillar Aβ42. Some microtubule loss (65% polymerized) was observed after a comparable exposure to fibrillar Aβ42, but only at the much higher total peptide concentration of 3 μM.

Tau was found to be required for microtubule disassembly in primary hippocampal neurons induced by prefibrillar Aβ42. Neurons were treated with siRNA to reduce tau expression to trace levels (Fig. 2 D and Fig. S2, available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1). After 2 h of exposure to 2 μM prefibrillar Aβ42, the level of polymerized tubulin remained nearly unchanged in tau-deficient neurons (~20% soluble tubulin), whereas the tau-expressing neurons again showed an increase in soluble tubulin (~60% soluble tubulin). It was not possible to determine how much tau was microtubule bound or soluble in these experiments, because the tau was quantitatively solubilized by the Triton X-100 under conditions in which the polymerized tubulin was resistant to extraction (Black et al., 1996). Thus, the results for tubulin demonstrate that the endogenous tau in neurons, like transfected tau in CV-1 cells, makes microtubules acutely sensitive to prefibrillar Aβ42.

Treatment of tau-expressing neurons with prefibrillar Aβ42 under conditions that induced microtubule disassembly did not cause increased AD-like tau phosphorylation at any of several sites (Fig. 3). This was found by immunoblotting using phosphorylation-sensitive monoclonal anti-tau antibodies: PHF-1, AT180, and tau-1. Although many additional AD-like

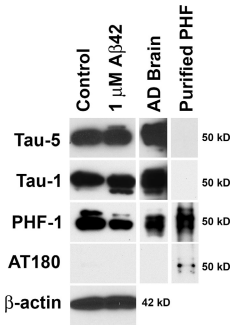

Figure 3. **Prefibrillar Aβ42 does not induce AD-like tau phosphorylation.** Primary rat hippocampal neurons were treated with 1 μM Aβ42 for 2 h before Western blotting with the indicated anti-tau antibodies: PHF-1 (phosphoserine 396 and 404), AT180 (phosphoserine 231), and tau-1 (dephosphoserine 199 and 202). The phosphorylation of tau in treated neurons was compared with whole brain extract from an AD brain, as well as to paired helical filaments purified from an AD brain. Note that AD-like tau phosphorylation was not increased by prefibrillar Aβ42.

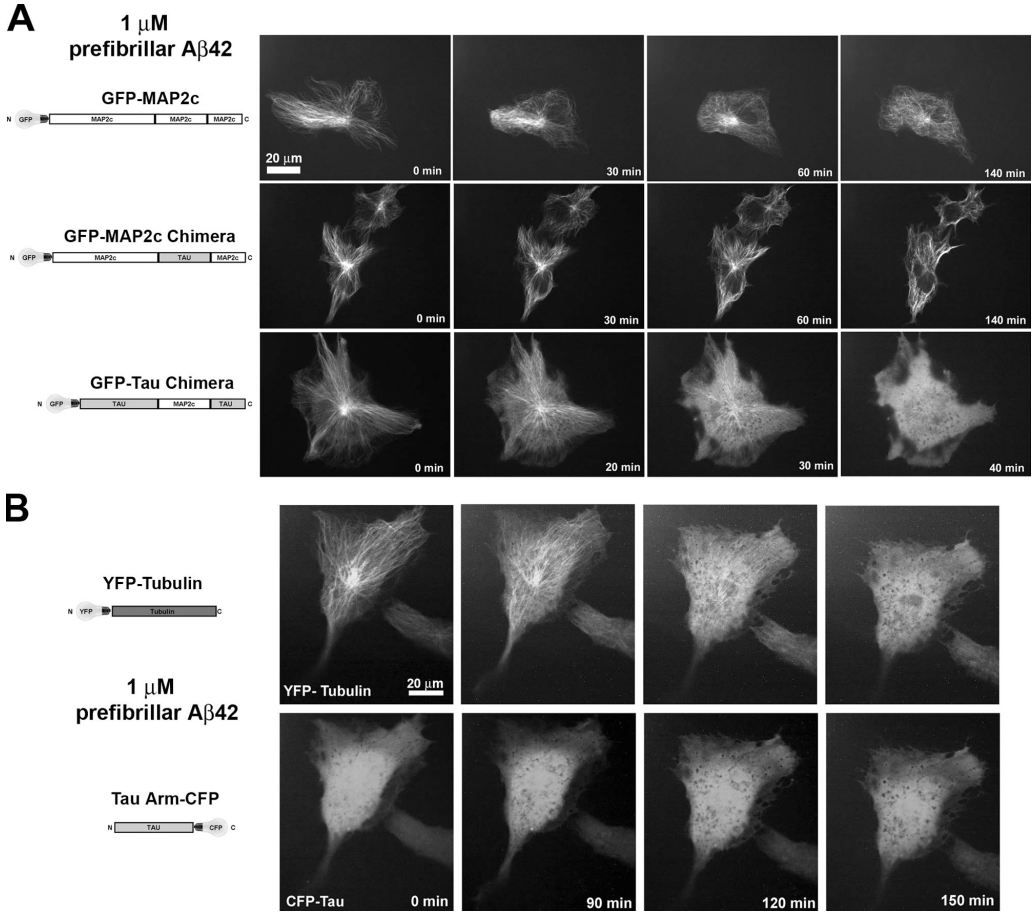

Figure 4. **The active portion of tau resides within an N-terminal fragment that does not target to microtubules.** CV-1 cells transfected with the indicated fluorescently tagged proteins were treated with 1 μM prefibrillar Aβ42 and imaged by time-lapse fluorescence microscopy. (A) Microtubules remained intact in cells expressing GFP-MAP2c or GFP-MAP2c chimera after >2 h of exposure to Aβ42. In contrast, microtubules depolymerized in cells expressing GFP-tau chimera after <1 h of exposure to Aβ42. (B) Microtubules also depolymerized in cells that were exposed to Aβ42 and expressed the N-terminal arm of tau coupled to CFP.

phosphorylation sites remain to be examined, these data suggest that conversion of tau to an AD-like phosphorylation state does not underlie the release of tau from microtubules and subsequent microtubule disassembly induced by prefibrillar Aβ42.

The specificity of tau for microtubule loss in cells treated with prefibrillar Aβ42 was shown by expressing GFP-tagged MAP2c in CV-1 cells. MAP2c is a neuron-specific microtubule-associated protein with a microtubule binding domain ∼70% identical to that of tau's (Dehmelt and Halpain, 2005). 3 h of exposure to prefibrillar Aβ42 did not cause any apparent loss of microtubule integrity in cells. A region of tau responsible for conferring sensitivity to Aβ42 was mapped using a combination of tau/MAP2c chimeric proteins and a CFP-tagged tau fragment. Only cells expressing "tau chimera," a GFP-tagged protein comprising the microtubule binding domain of MAP2c flanked by the N-terminal arm and C-terminal tail of tau (Fig. 4 B and Videos 5–7, available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1) responded to the addition of prefibrillar Aβ42. Similar activity was observed when the tau projection domain-CFP, which did not localize on microtubules, was expressed in cells that subsequently were treated with prefibrillar Aβ42 (Fig. 4 B and Video 8). The qualitative results shown in Fig. 4 and Videos 1 and 4–8 were confirmed by quantitation of fluorescence micrographs for microtubule-containing cells before and after 3 h of exposure to prefibrillar Aβ42 (Fig. 5). The N-terminal half of tau therefore responds to prefibrillar Aβ42 and does not have to target to microtubules to exert its effects. Furthermore, the closely related neuronal microtubule protein, MAP2c, cannot substitute for tau at promoting microtubule disassembly in cells exposed to prefibrillar Aβ42.

The nature of the functional connection between Aβ and tau has been one of the most enduring and intractable mysteries in AD research, and solving this mystery is bound to open potential new avenues of early detection and therapeutic intervention for AD. The results presented here represent the swiftest and most deleterious tau-dependent effects of Aβ that have yet been described. When considered together with recently published studies demonstrating localization of oligomeric Aβ in AD brain at sites distinct from classic amyloid plaques (Kayed et al., 2003), a critical role for oligomeric Aβ in memory loss (Lesne et al., 2006), and colocalization of Aβ with tau in tangle-bearing AD neurons in vivo (Guo et al., 2006), the present results suggest a mechanism by which Aβ and tau conspire coordinately to compromise neuronal function. Diminished

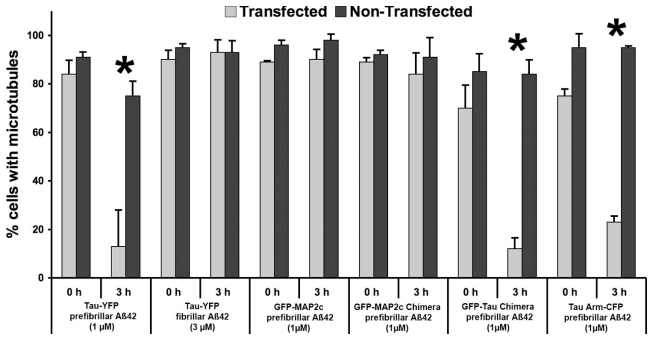

Figure 5. **Quantitation of fluorescence micrographs for Aβ42-induced microtubule loss.** CV-1 cells expressing the indicated proteins with 40–50% transfection efficiency were exposed to the form of Aβ42 specified on the figure. The cells were then fixed and stained with anti-tubulin and scored for microtubules as described in Materials and methods. Transfected and nontransfected refer to cells that did and did not express the indicated transgenes, respectively. Error bars indicate the SD, and asterisks mark statistically significant differences at $\alpha = 0.02$ between the indicated pairs of transfected and nontransfected cells after 3 h of Aβ exposure. Statistically significant differences were not found for any pair of transfected versus nontransfected cells at 0 h, nor for any nontransfected pair at 0 versus 3 h. The collective results shown here confirm the qualitative results shown in Figs. 1 and 4 and Videos 1 and 4–8 (available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1).

microtubule integrity could hinder essential microtubule functions, such as axonal transport, which is required to maintain synapses, and delivery of exocytotic membranes to the cell surface to repair plasma membrane holes (Shen et al., 2005) known to be induced by oligomeric Aβ (Kayed et al., 2003). The biochemical steps that underlie tau-dependent microtubule poisoning by prefibrillar Aβ remain unknown, but direct binding of tau to Aβ has been reported (Guo et al., 2006) and thus represents one possible step. Nevertheless, we have been unable to demonstrate specific coimmunoprecipitation of tau and Aβ out of tau-expressing cells exposed to prefibrillar Aβ42.

That the combination of prefibrillar Aβ and nonfilamentous tau were able to elicit such a dramatic disruption of microtubules supports the hypothesis that fibrillar forms of tau and Aβ are at least somewhat neuro-protective, because they sequester more dangerous, nonfibrillar forms of Aβ and tau (Tanzi, 2005). The fact that tau is required for Aβ-induced microtubule loss could explain, at least in part, why neurons, the principal tau-expressing cell type, are the cellular targets for destruction in AD. Moreover, the model presented here does not preclude other toxic functions of prefibrillar or fibrillar Aβ or filamentous tau, such as tau-dependent degeneration of cultured neurons induced by fibrillar Aβ40 (Rapoport et al., 2002) or toxicity related to intracellular tau filament accumulation (Khlistunova et al., 2006). Nevertheless, the rapid, tau-dependent destruction of microtubules that we observed to be induced by submicromolar concentrations of prefibrillar Aβ42 suggests that this process is one of the seminal events in AD pathogenesis at the cellular level.

Materials and methods

Antibodies

Tau-5, Tau-1, and R1 anti-tau antibodies were gifts from L. Binder (Northwestern University Medical School, Chicago, IL), and PHF-1 anti-tau was provided by P. Davies (Albert Einstein College of Medicine, New York, NY). AT180 anti-tau (Pierce Chemical Co.), DM1A anti-α-tubulin (Sigma-Aldrich), C4 anti-actin (Chemicon), 6E10 anti-Aβ (Signet; recognizes all forms of Aβ40 and Aβ42), fluorescently tagged goat anti–mouse IgG and goat anti–rabbit (Southern Biotechnology Associates, Inc.) and HRP-labeled goat anti–mouse IgG (KPL) were acquired from the indicated commercial sources. I-11 is one of the Glabe laboratory's rabbit polyclonal antibodies against oligomeric Aβ (Kayed et al., 2003).

Cell culture

CV-1 (African green monkey kidney) cells were cultured in DME (Invitrogen) supplemented with 10% Cosmic Calf Serum (Hyclone) and 50 μg/ml gentamycin. Cells were transiently transfected using Fugene (Roche) or a nucleofector (Amaxa) with cDNAs for the longest human isoform of tau or the projection domain (amino acids 1–248) of tau linked at their C terminals to ECFP or EYFP (CLONTECH Laboratories, Inc.); with YFP–α-tubulin (CLONTECH Laboratories, Inc.); or with MAP2c or MAP2c/tau chimeras (Roger et al., 2004) tagged at their N termini with GFP, which were gifts from S. Halpain (The Scripps Research Institute, La Jolla, CA). For nucleofection, program A-033 and solution V were used according to the manufacturer's instructions. Primary cortical neurons were purchased from Genlantis and cultured according to their guidelines. Primary hippocampal neurons (Wisco et al., 2003) were grown for at least 8 d before Aβ treatment. The tau siRNA (SMARTpool; Dharmacon) and control scrambled siRNA (Nonspecific duplex II; Dharmacon) were transfected into primary hippocampal neurons by nucleofection using the rat neuron solution (Amaxa) and program G-13 (Qiang et al., 2006). Cells were cultured for 4 d after nucleofection and were then exposed to Aβ.

Aβ treatment

Previously described methods were used to synthesize (Burdick et al., 1992) and resuspend (Kayed et al., 2003) Aβ42 and Aβ40. The Aβ was added to cells cultured in serum-free DME to final concentrations from 0.1 to 5 μM. Prefibrillar Aβ was used in the first and second days after resuspension, whereas fibrillar Aβ was used after at least 7 d of stirring.

Microscopy

Live cell imaging and immunofluorescence microscopy were performed as previously described (Mateer et al., 2002) on an Axiovert 100 (Carl Zeiss MicroImaging, Inc.) equipped with 63× 1.4 NA planapo and 25× 0.8 NA plan-neofluar objectives (Carl Zeiss MicroImaging, Inc.), a CARV spinning disk confocal head (BD Biosciences), an X-Cite 120 illuminator (EXFO Photonic Solutions), a cooled charge-coupled device (Orca ER; Hamamatsu), and OpenLab software (Improvision) for image acquisition and processing. For live cell time-lapse imaging, the cells were maintained on the microscope stage in DME at 37°C in an atmosphere of 95% air and 5% CO_2. The supplemental time-lapse videos were produced by first using the public domain software, ImageJ to pseudocolor eight-bit grayscale images stacks to eight-bit cyan, green, or yellow image stacks, and then using QuickTime Pro 7 and Keynote 3 (Apple) to produce self-playing videos compressed with the H.264 codec. For electron microscopy, primary cortical and hippocampal neurons were grown on glass coverslips, treated with Aβ42, and fixed in 2.5% glutaraldehyde plus 0.5% tannic acid in 0.1 M cacodylate buffer, pH 7.4. Cells on coverslips were dehydrated and capsule embedded in EPON, and the glass coverslip was removed from the EPON by alternating liquid nitrogen and warm water submersion of the capsule. Sectioned samples were viewed on an electron microscope (JEM 1010; JEOL) at 80 kV, and images were captured using a 16-megapixel cooled charge-coupled device (SAI-12c; Scientific Instruments and Applications, Inc).

Quantitation of fluorescence micrographs

Nucleofection was used to express fusion proteins of CFP, GFP, or YFP coupled to tau, the N-terminal tau arm, MAP2c, or MAP2c/tau chimeras in CV-1 cells growing on glass coverslips. Cultures that either were or were not exposed to prefibrillar or fibrillar Aβ42 for 3 h were fixed and permeabilized for 5 min in −20°C methanol and stained for immunofluorescence with anti–α-tubulin followed by TRITC-labeled goat anti–mouse IgG. For each coverslip, six randomly chosen fields of view were photographed separately in both the TRITC channel and the CFP, GFP, or YFP channel using the 25× objective. Typically, 40–50% of the total cells expressed the transfected protein. Next, without knowing the identity of the sample, an observer counted the total cells and microtubule-containing cells in one anti-tubulin field and then counted the total number of transfected cells and microtubule-containing transfected cells in the same field. This process was

repeated for the remaining fields of the coverslip, and the results from all six fields, which comprised ~500 total cells, were merged into a single dataset. Each such experiment was performed in triplicate, and the net results were graphed in Figs. 1 E and 5 as the mean ± SD of the percentage of microtubule-containing transfected and nontransfected cells for each experimental condition. For Fig. 5, pairwise comparisons were made of transfected versus nontransfected cells at 0 and 3 h of Aβ exposure and of nontransfected cells at 0 versus 3 h of Aβ exposure.

Biochemical quantitation of unassembled and polymerized tubulin

CV-1 cells and primary hippocampal neurons were treated with 1–3 μM prefibrillar or fibrillar Aβ42. Cells were washed briefly with PBS and extracted with PHEM buffer (60 mM Pipes, pH 6.9, 25 mM Hepes, 10 mM EGTA, and 2 mM $MgCl_2$) with 10 μM taxol and 0.2% Triton X-100 for 5 min. The buffer was collected and centrifuged for 5 min at maximum speed in a table top centrifuge (model 5415; Eppendorf), and the supernatant was removed and mixed with 1/5 volume of 6× sample buffer for SDS-PAGE to generate a Triton-soluble fraction. An equivalent volume of PHEM buffer and 6× sample buffer was added to the dish, and this sample was added to the pellet from the spin to create a Triton-insoluble fraction. Equal volumes of Triton-soluble and -insoluble fractions, which contained soluble and polymerized tubulin, respectively (Black et al., 1996), were then analyzed by immunoblotting with anti–α-tubulin. Quantitation of scanned immunoreactive bands was performed using ImageJ.

Online supplemental material

Fig. S1 shows dot blots of prefibrillar and fibrillar Aβ42 and control proteins. Fig. S2 shows a Western blot of cell lysates from the scrambled siRNA- and tau siRNA–treated hippocampal neurons. Video 1 shows that microtubules disassemble in tau-expressing CV-1 cells exposed to prefibrillar Aβ42. Video 2 shows that microtubules disassemble in tau- expressing CV-1 cells exposed to prefibrillar Aβ40. Video 3 shows that tau is required for prefibrillar Aβ42 to induce microtubule disassembly. Video 4 demonstrates that fibrillar Aβ42 does not induce microtubule disassembly in tau-expressing cells. Video 5 shows that prefibrillar Aβ42 does not induce microtubule disassembly in MAP2c-expressing cells. Video 6 demonstrates that prefibrillar Aβ42 does not induce microtubule disassembly in cells expressing MAP2c chimera. Video 7 shows that prefibrillar Aβ42 induces microtubule disassembly in cells expressing tau chimera. Video 8 demonstrates that prefibrillar Aβ42 induces microtubule disassembly in cells expressing the N-terminal tau arm. Online supplemental material is available at http://www.jcb.org/cgi/content/full/jcb.200605187/DC1.

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