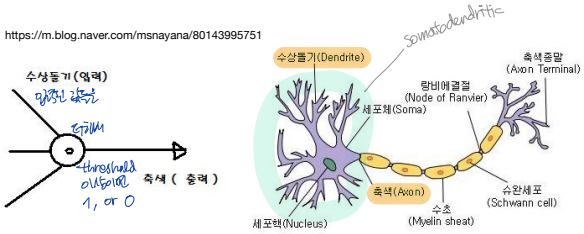

Amyloid-β and tau — a toxic *pas de deux* in Alzheimer's disease

Lars M. Ittner and Jürgen Götz

Abstract | Amyloid-β and tau are the two hallmark proteins in Alzheimer's disease. Although both amyloid-β and tau have been extensively studied individually with regard to their separate modes of toxicity, more recently new light has been shed on their possible interactions and synergistic effects in Alzheimer's disease. Here, we review novel findings that have shifted our understanding of the role of tau in the pathogenesis of Alzheimer's disease towards being a crucial partner of amyloid-β. As we gain a deeper understanding of the different cellular functions of tau, the focus shifts from the axon, where tau has a principal role as a microtubule-associated protein, to the dendrite, where it mediates amyloid-β toxicity.

Reflecting an aging population, for most societies dementia is becoming a major health burden. In 2009, 35.6 million cases of Alzheimer's disease were recorded worldwide, a number that is estimated to be more than doubled by 2050. A cure for Alzheimer's disease and related forms of dementia is lacking, and current treatments are limited to modest symptomatic relief (reviewed in REFS 1,2).

The brains of patients with Alzheimer's disease, in addition to showing nerve and synapse loss, are histopathologically characterized by two hallmark lesions — amyloid-β-containing plaques and neurofibrillary tangles (NFTs), which are composed of hyperphosphorylated forms of the microtubule-associated protein tau[3]. Tau pathology in the absence of overt amyloid-β pathology is characteristic of a subset of frontotemporal dementia (FTD; also termed frontotemporal lobar degeneration, FTLD), which is the second most prevalent form of dementia occurring before the age of 65 (REF. 4). Progression of NFT pathology throughout the brain (a process that has been called 'spreading') correlates with disease progression in Alzheimer's disease[5], and loss of synapses is one of the earliest events that has been associated with functional impairment[6].

In a small subset of familial Alzheimer's disease (FAD) cases, mutations have been identified in genes that encode the amyloid precursor protein (APP), presenilin-1 (PS1) or PS2 (REF. 7). The tau-encoding microtubule-associated protein tau (*MAPT*; also known as *tau*) gene carries mutations in a subset of familial forms of FTD[8], establishing a prominent role for tau in neurodegenerative disease[8]. In sporadic Alzheimer's disease (SAD), polymorphisms of apolipoprotein E4 (*APOE4*) and other genes have been associated with an increased risk of developing the disease[7]. The identification of these pathogenic mutations in people with Alzheimer's disease and FTD has assisted in the generation of a plethora of transgenic animal models (reviewed in REF. 9). However, it is important to keep in mind that the vast majority of Alzheimer's disease cases are sporadic, with the underlying cause (or causes) remaining mysterious, and that current animal models of Alzheimer's disease are not complete models of the human disease, but rather, model key aspects of it.

Substantial progress has been made more recently in understanding pathogenic mechanisms, such as the spreading of tau (and other proteins with toxic properties) between neurons and across brain regions (reviewed in REF. 10). Furthermore, human, mouse and *in vitro* studies have revealed a direct link between amyloid-β and tau in causing toxicity in Alzheimer's disease[11], but the molecular nature of this interplay has remained unsolved, though it has been a key question in the field for over a decade. This Progress article reviews recent findings that have shed light on the complex interaction between amyloid-β and tau, in particular at the synapse, and on how this interaction is related to the pathogenesis of Alzheimer's disease.

Amyloid-β toxicity at synapses

Step-wise cleavage of APP results in the formation of the 39 to 42 amino-acid peptide amyloid-β[12,13]. Amyloid-β is prone to aggregation, giving rise to toxic species, including dimers, oligomers and fibrils[14]. Although there remains controversy about which of the amyloid-β forms (dimers, oligomers or fibrils) is the toxic species, there is a general agreement that synapses — in particular the postsynaptic compartment — are the prime targets of amyloid-β toxicity[6]. Accordingly, acute amyloid-β treatment causes synapse and spine loss, induces long-term depression (LTD) and impairs long-term potentiation (LTP) in several experimental paradigms[15]. Although there might be a single receptor that mediates amyloid-β toxicity at the postsynaptic compartment, it seems more likely that several postsynaptic receptors are involved, such as prion proteins, α7-nicotinergic receptors, metabotropic glutamate receptors (mGluRs) and, in particular, NMDARs[15–17]. The toxicity mediated by a particular receptor may not necessarily involve direct binding of amyloid-β to the receptor, but could be due to an indirect modulation of receptor properties by amyloid-β, possibly through membrane association — this may explain why amyloid-β has been reported to bind to distinct receptors under certain conditions and not others, depending on the experimental design[18,19].

Excitotoxicity due to over-excitation of NMDARs has been implicated as a central mechanism by which amyloid-β causes neuronal damage, despite a lack of evidence for a direct binding of amyloid-β to NMDARs[20]. Interestingly, NMDARs mediate amyloid-β-induced spine loss, whereas under identical experimental conditions, mGluRs mediate amyloid-β-induced LTD[15], suggesting that different receptors mediate different aspects of amyloid-β toxicity. A role of NMDARs in

Prion: 유전자를 가지지 않았음에도 증식(增殖)하고 감염력을 가지는, 바이러스보다 작은 병원체. 1980년대 초에 발견되었으나 아직 완전히 해명되지 않음.

Excitotoxicity refers to an excessive activation of neuronal amino acid receptors.

amyloid-β toxicity is further supported by the beneficial effects of the partial NMDAR antagonist memantine in patients with Alzheimer's disease[1].

Tau — novel functions beyond the axon

Tau contains three major domains: an amino-terminal projection domain, a carboxy-terminal domain of microtubule-binding (MTB) repeats and a short tail sequence. In the human brain, there are six tau isoforms, resulting from alternative splicing of exons 2, 3 (which are N-terminal inserts) and 10. Exon 10 encodes an additional MTB repeat, resulting in isoforms with either three or four MTB repeats (reviewed in REFS 8,21).

Tau is predominantly found in axons, owing to an incompletely understood sorting mechanism[22–25]. Under physiological conditions, tau has also been localized to dendrites, although levels there are much lower[26]. The best-established functions of tau are thought to be the stabilization of microtubules and the regulation of motor-driven axonal transport[27]. Less well understood functions involve an interaction of tau with the membrane cortex[26,28]. A further compartment in which tau has been found is the somatodendritic domain; tau is localized here under pathological conditions, as discussed below.

Tau has as many as 84 putative phosphorylation sites, of which 45 are serines, 35 threonines, and 4 tyrosines. It is more highly phosphorylated during development than in mature neurons[29]. How phosphorylation influences tau function is only poorly understood, but it negatively regulates the binding of tau to microtubules. In patients with Alzheimer's disease or FTD, as well as in tau transgenic mouse models, tau becomes increasingly phosphorylated (that is, hyperphosphorylated) — owing to incompletely understood mechanisms — at both physiological and 'pathological' phosphorylation sites, which causes it to detach from microtubules[8]. Hence, functions of tau that involve microtubules, such as microtubule stabilization and the regulation of axonal transport[27], may be compromised, possibly contributing to disease. Hyperphosphorylated tau accumulates in the somatodendritic compartment of neurons, aggregates and eventually forms NFTs[30]. There is good evidence that soluble hyperphosphorylated tau contributes to neuronal dysfunction before its deposition[31]. Indeed, hyperphosphorylated tau has been shown to interfere with neuronal functions, such as mitochondrial respiration and axonal transport[27,32].

Is tau a postsynaptic scaffolding protein?

Tau interacts with tubulin via its MTB repeats, whereas its projection domain mediates interactions with other partners, such as the tyrosine protein kinase FYN[26,33] and dynactin[34]. The dynactin–tau interaction is involved in intracellular transport

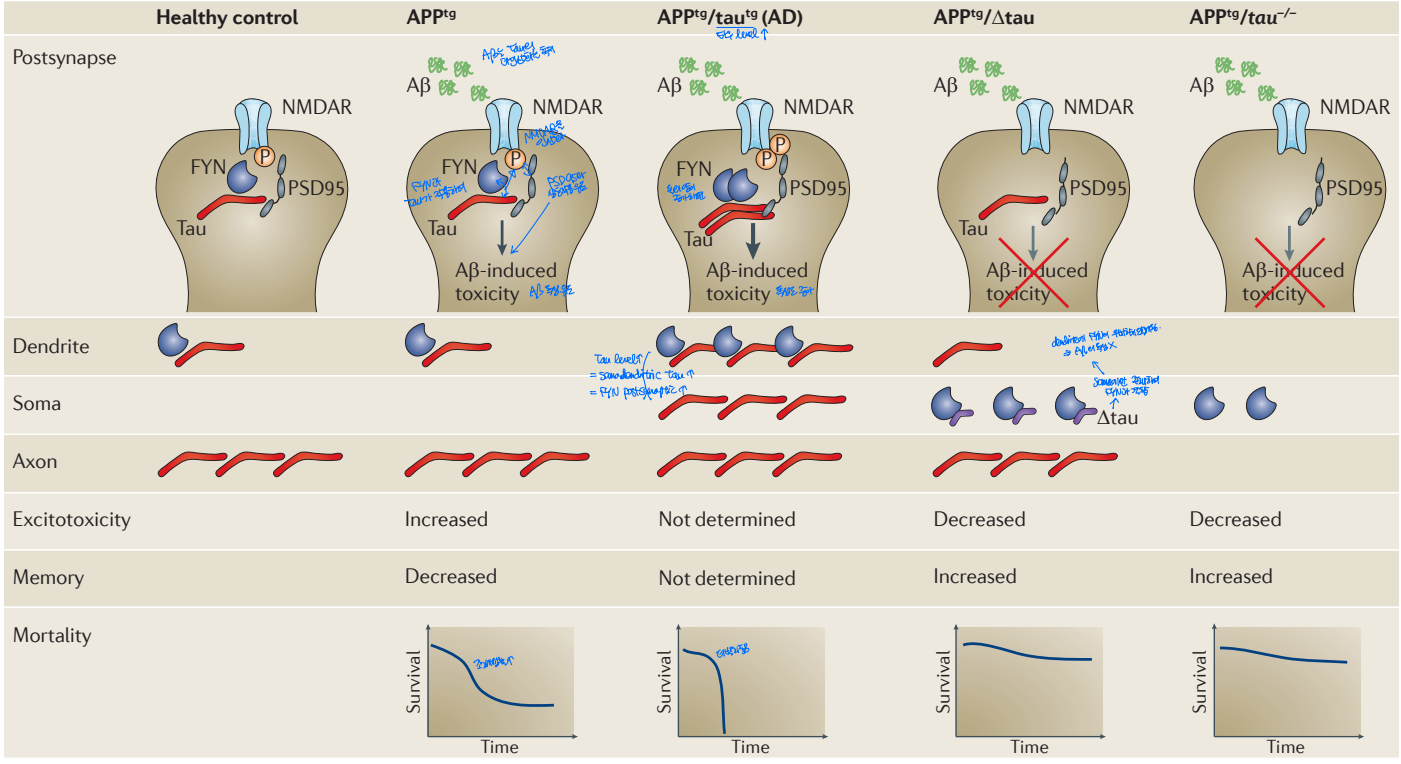

Figure 1 | **Disrupting tau-dependent dendritic targeting of FYN protects neurons from amyloid-β toxicity in mouse models of Alzheimer's disease.** Under physiological conditions, tau is found in the axon and, at lower levels, in dendrites of CNS neurons. Upon interaction with tau, the tyrosine protein kinase FYN is localized to the dendritic compartment, where it phosphorylates NMDA receptors (NMDARs) and thereby mediates their interaction with postsynaptic density protein 95 (PSD95) — an interaction required for amyloid-β (Aβ) toxicity in Alzheimer's disease and in amyloid precursor protein (APP) transgenic (APP^{tg}) mice, resulting in excitotoxicity, memory deficits and premature mortality. Increased levels of tau in transgenic mice (tau^{tg}) result in accumulation of tau in the soma and dendrite of neurons, together with increased postsynaptic FYN levels. This is associated with increased amyloid-β toxicity in double transgenic APP^{tg}/tau^{tg} mice (shown by a thick arrow), which show an early mortality compared with APP^{tg} mice. Truncated tau (Δtau) that lacks microtubule binding properties does not localize to dendrites, but interacts with FYN in the soma. In a dominant-negative manner, Δtau acts on the tau–FYN interaction, thereby preventing FYN from accessing dendrites, which consequently protects APP^{tg}/Δtau mice from amyloid-β toxicity. Depletion of tau by gene knockout ($tau^{-/-}$) prevents tau-dependent localization of FYN to dendrites and hence, protects APP^{tg}/$tau^{-/-}$ mice from amyloid-β toxicity. Differences in the mechanism by which FYN is retained in the soma of $tau^{-/-}$ and Δtau neurons may explain the additive protective effects seen in APP^{tg}/$tau^{-/-}$/Δtau mice. AD, Alzheimer's disease.

and/or in linking actin and microtubules[34]. The functional relevance of the FYN–tau interaction *in vivo* remained mysterious until recently, although its relevance was revealed *in vitro* as early as 1998 (REF. 33). Interestingly, both phosphorylation of tau and expression of pathogenic mutations in *MAPT* result in a stronger interaction of tau with FYN *in vitro*[35], suggesting that it might be relevant to disease. The FYN–tau interaction facilitates the targeting of FYN to postsynaptic sites (that is, dendrites) *in vivo* — a targeting markedly reduced in tau knockout (*tau*$^{-/-}$) mice — and FYN subsequently accumulates in the soma[26] (FIG. 1). At postsynaptic sites, FYN phosphorylates the NMDAR subunit 2B (NR2B), thereby mediating complex formation of NMDARs with the postsynaptic density protein 95 (PSD95)[36]. This NMDAR–PSD95 interaction is required for excitotoxic downstream signalling[36]. As a consequence of the reduced NMDAR–PSD95 interaction[26], *tau*$^{-/-}$ mice are less susceptible to both experimental seizures and amyloid-β toxicity[20,26] (FIG. 1) .

Importantly, enhanced immunohistochemistry methods have revealed the presence of tau in dendrites under physiological conditions[26]. This localization depends on the MTB repeats, and therefore most likely on microtubule binding, as truncated tau that lacks the MTB repeats (Δtau) and consequently does not bind tubulin, does not access dendrites *in vivo*[26] (FIG. 1). Δtau also acts dominant-negatively on the tau-mediated dendritic targeting of FYN and so reproduces the effects of a *tau*$^{-/-}$ on NMDAR-mediated signalling, including mitigation of amyloid-β toxicity[26] (FIG. 1). Together with increasing evidence for the dynamic presence of microtubules in dendritic spines — a feature linked to synaptic plasticity (reviewed in REF. 37) — these data raise the possibility that tau has important scaffolding functions in the postsynaptic compartment in healthy neurons. This notion is also supported by the strong interaction of tau with PSD95 (REF. 26), a protein that itself is a postsynaptic scaffolding protein involved in NMDAR downstream signalling[36] (FIG. 1). In summary, although tau is predominantly found in axons, it has newly discovered dendritic functions that are pivotal in healthy neurons and that, when disturbed, seem to have a role in disease.

Linking amyloid-β and tau

According to the amyloid cascade hypothesis, amyloid-β formation is the critical step in driving Alzheimer's disease pathogenesis[11]. Support for this concept stems from the identification of pathogenic mutations in patients with FAD that are linked to amyloid-β formation, as well as increased amyloid-β levels and a higher frequency of Alzheimer's disease in people with trisomy 21, who carry an additional *APP* allele[7]. Therefore, a crucial question is where tau is to be placed in the amyloid cascade. Is it a prime target, a mediator or a kind of bystander of amyloid-β toxicity? Although amyloid-β and tau exert toxicity through separate mechanisms[38], evidence from both *in vitro* and *in vivo* models suggests that there are three possible modes of interaction between the two (FIG. 2).

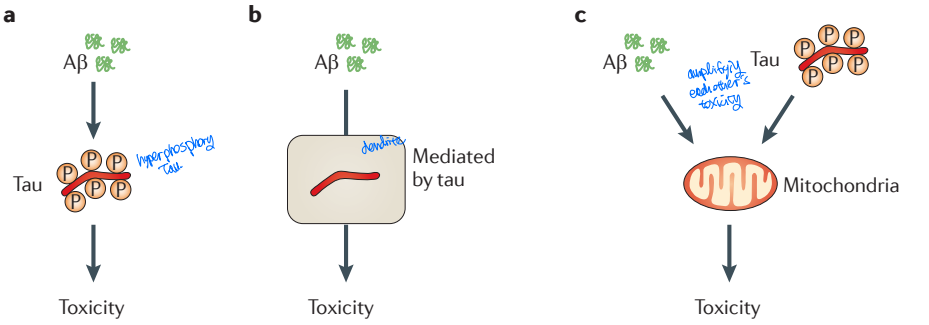

Figure 2 | **Amyloid-β and tau: three possible modes of interaction. a** | Amyloid-β (Aβ) drives tau pathology by causing hyperphosphorylation of tau, which in turn mediates toxicity in neurons. **b** | Tau mediates amyloid-β toxicity and hence, amyloid-β toxicity is critically dependent on the presence of tau — for example, in the dendrite. **c** | Amyloid-β and tau target cellular processed or organelles synergistically, thereby possibly amplifying each other's toxic effects.

Amyloid-β drives tau pathology. A hierarchical mode of amyloid-β acting on tau is supported by several lines of evidence. Amyloid-β formation in APP transgenic mice causes hyperphosphorylation of tau, whereas there is no overt amyloid-β plaque pathology in tau transgenic mice[39]. In offspring of APP transgenic mice crossed with tau transgenic mice the NFT pathology, but not amyloid-β plaque pathology, is exacerbated[40,41] (TABLE 1). Similarly, intracranial injection of synthetic amyloid-β into mutant tau transgenic mice aggravates NFT pathology[42]. Furthermore, immunization against amyloid-β in triple transgenic mice (3xTg-AD mice) that have combined plaque and NFT pathology resulted in reduced levels of hyperphosphorylated tau[43]. Interestingly, recent studies have shown the same mode of induction of NFT pathology by other amyloidogenic proteins, such as integral membrane protein 2B (also known as the Bri peptide), which aggregates in patients with familial British or Danish dementia[44], suggesting a general induction of NFT formation by amyloidogenic peptides rather than a specific mechanism for amyloid-β.

Synergistic toxic effects of amyloid-β and tau. In causing downstream toxicity, amyloid-β and tau have been shown to target different components of the same system, thereby amplifying each other's toxic effects. A good example for this mode of interplay is the mitochondrial dysfunction that occurs in mouse models of Alzheimer's disease, a pathogenic mechanism that is increasingly recognized to have a role in neurodegeneration[3]. Amyloid-β and tau both impair mitochondrial respiration in triple transgenic mice (^{triple}AD mice) that display both amyloid-β and tau pathologies[45]. Interestingly, tau preferentially impairs complex I of the respiratory chain, whereas amyloid-β blocks complex IV-dependent respiration, and this leads to an aggravated mitochondrial impairment in mice with combined tau and amyloid-β pathologies, compared with mice overexpressing tau or APP alone[45].

Tau mediates amyloid-β toxicity. The view that tau plays a mere 'secondary' role in amyloid-β toxicity has been substantially challenged by the observation that *tau*$^{-/-}$ neurons are protected from amyloid-β-induced cell death in culture[46]. Importantly, this protection has been reproduced in two independent *in vivo* studies, using different APP transgenic and tau-deficient mouse strains[20,26] (TABLE 1). One study showed that protection from amyloid-β-induced toxicity in animals lacking tau was due to a reduced dendritic localization of FYN, resulting in a reduced interaction of NMDARs with PSD95 and, as a consequence, reduced amyloid-β-mediated excitotoxicity[26]. Importantly, the level of protection against amyloid-β-induced toxicity that was observed in tau$^{-/-}$ or Δtau74 mice (which express Δtau in neurons) could also be achieved by disrupting the NMDAR–PSD95 interaction with a therapeutic

Table 1 | **Combinatorial amyloid–tau mouse studies**

Year	Amyloid model	Tau model	Phenotype in double or triple tg mice	Refs
2001	Tg2576 (K670N/M671L-APP$_{695}$)	JNPL3 (P301L-(0N4R) tau)	(p-tau, NFTs)	40
2001	Synthetic Aβ$_{1-42}$	pR5 (P301L-(2N4R) tau)	(p-tau, NFTs)	42
2003	3xTg AD (K670N/M671L-APP$_{695}$ + M146V-PS1)	(P301L-(0N4R) tau)	Combined amyloid-β and tau pathology	62
2007	APP23 (K670N/M671L-APP$_{751}$)	JNPL3 (P301L-(0N4R) tau) on C57Bl/6	(p-tau, NFTs); late onset pathology	63
2007	J20 (K670N/M671L/V717F-APP$_{751}$)	*Tau*$^{-/-}$	Prevents memory deficits and premature deaths of J20 line	20
2007	J20 (K670N/M671L/V717F-APP$_{751}$)	*Tau*$^{-/-}$	Prevents amyloid-β-induced NPY expression and calbindin loss in hippocampus	64
2008	APP-V717I (V717I-APP$_{695}$)	tau-P301L (P301L-(2N4R) tau)	(p-tau), increased GSK3β activity	41
2010	APP152 (K670N/M671L-APP$_{751}$ + N141I-PS2)	pR5 (P301L-(2N4R) tau)	(p-tau, NFTs)	65
2010	Tg2576 (K670N/M671L-APP$_{695}$)	*Tau*$^{-/-}$	Increased memory deficits in aged mice	52
2010	ADnnPP7 (795InsTTTAATTTGT-BRI2)	TauP301S	(p-tau, NFTs)	44
2010	APP23 (K670N/M671L-APP$_{751}$)	pR5 (P301L-(2N4R) tau)	Increased premature death rate	26
2010	APP23 (K670N/M671L-APP$_{751}$)	*Tau*$^{GFP/GFP}$ (GFP knock-in)	Prevents memory deficits and premature death of APP23 line	26
2010	APP23 (K670N/M671L-APP$_{751}$)	Δtau74 (1-255aa tau)	Prevents memory deficits and premature deaths of APP23 line	26

Aβ, amyloid β; APP, amyloid precursor protein; GFP, green fluorescent protein; GSK3β, glycogen synthase kinase 3β; NFTs, neurofibrillary tangles; NPY, neuropeptide Y; p-tau; phosphorylated tau; tg; transgenic.

peptide[26]. This suggests that tau-dependent dendritic signalling is pivotal in mediating amyloid-β toxicity. Interestingly, tau reduction also prevents amyloid-β-induced defects in axonal transport of mitochondria and other cargos[47] — another example of how tau mediates amyloid-β toxicity.

A note on tau*$^{-/-}$ *mice. When the first *tau*$^{-/-}$ mice were reported, the absence of a pronounced phenotype came as a surprise[48,49]. In one *tau*$^{-/-}$ strain, tubulin spacing in axonal microtubules was only slightly altered[48], and primary neuronal cultures obtained from a second *tau*$^{-/-}$ strain revealed a slightly delayed axonal outgrowth[49], possibly due to compensation of microtubule stabilization by microtubule-associated protein 1A (MAP1A)[48]. A similarly delayed early axon formation was observed in cultured neurons obtained from a third tau-deficient strain (L.M.I. and J.G., unpublished observations), in which green fluorescent protein was introduced into the *MAPT* locus[50]. Interestingly, old, but not young, *tau*$^{-/-}$ mice present with behavioural changes that include aggression and memory deficits, which may suggest that compensatory mechanisms for lack of tau are functional early in life but might fail at higher age[51]. This may also explain the changes in pathology in aged offspring of APP transgenic Tg2576 mice crossed with *tau*$^{-/-}$ mice[52]. Whether this aggravation of deficits becomes relevant in the long-term outcome of tau-targeted treatment remains to be determined.

Tau axis hypothesis of Alzheimer's disease

Based on the recent findings of a dendritic function of tau and its role in mediating amyloid-β toxicity, and to highlight the central role of tau in disease, we postulate a novel 'tau axis hypothesis' that links amyloid-β and tau pathology in the dendritic compartment. This hypothesis consists of two parts.

First, postsynaptic toxicity of amyloid-β is tau-dependent. More precisely, tau interacts with FYN and thereby increases targeting and/or scaffolding of FYN to the postsynaptic compartment, where FYN links NMDARs to downstream signalling pathways (FIG. 1). This sensitizes NMDARs and makes them responsive to amyloid-β toxicity. This mode of tau-dependent amyloid-β toxicity in the dendritic compartment of neurons involves excitotoxic signalling.

Second, exposure of neurons to amyloid-β — and continued exposure in particular — has multiple toxic effects. Importantly, amyloid-β triggers progressively increased phosphorylation (hyperphosphorylation) of tau. As a consequence, tau binding to microtubules is compromised, causing tau to accumulate at an increasing pace in the somatodendritic compartment of diseased neurons (FIG. 3). Moreover, phosphorylated tau has an increased affinity for FYN[35]. Together, this results in high levels of postsynaptic FYN and sensitization of NMDARs, rendering neurons even more susceptible to amyloid-β toxicity in dendrites.

Thus, while the amyloid cascade hypothesis focuses on amyloid-β, the 'tau axis hypothesis' incorporates the essential role of tau by defining its novel functions in dendrites. Whether postsynaptic amyloid-β toxicity is linked to increased tau phosphorylation, thereby establishing a vicious circle, remains to be established. In addition, although evidence from mouse models of Alzheimer's disease suggests that dendritic amyloid-β toxicity is an early event in disease, its contribution to human disease needs to be established.

Interestingly, tau reduction also prevents amyloid-β-induced defects in axonal transport of mitochondria[47], which may link the 'tau axis hypothesis' to two additional hypotheses in the field: the 'axonal transport impairment' hypothesis, according to which tau induces failure of axonal transport[53,54]; and the 'oxidative stress' hypothesis, according to which mitochondria — being an essential axonal transport cargo — are functionally impaired, resulting in the production of reactive oxygen species[55].

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products.

Future directions

Although the roles of tau and its interactions with amyloid-β increasingly are being revealed, one of the important remaining questions pertains to the function of the six tau isoforms in the human brain. The finding that in mice, tau has a scaffolding function in dendrites suggests that there may be multiple scaffolding partners for tau in this

Endogeny 내인성
내인성은 다양한 문맥에서 내부에서 기원된 행동이나 물질을 나타낸다. 생물학에서는 생물체, 조직 또는 세포 내에서 유래된 물질을 뜻한다. 내인성 바이러스 요소는 생식 세포의 게놈에 조상 대대로 삽입되어 온 바이러스로부터 유래된 DNA 염기서열이다.

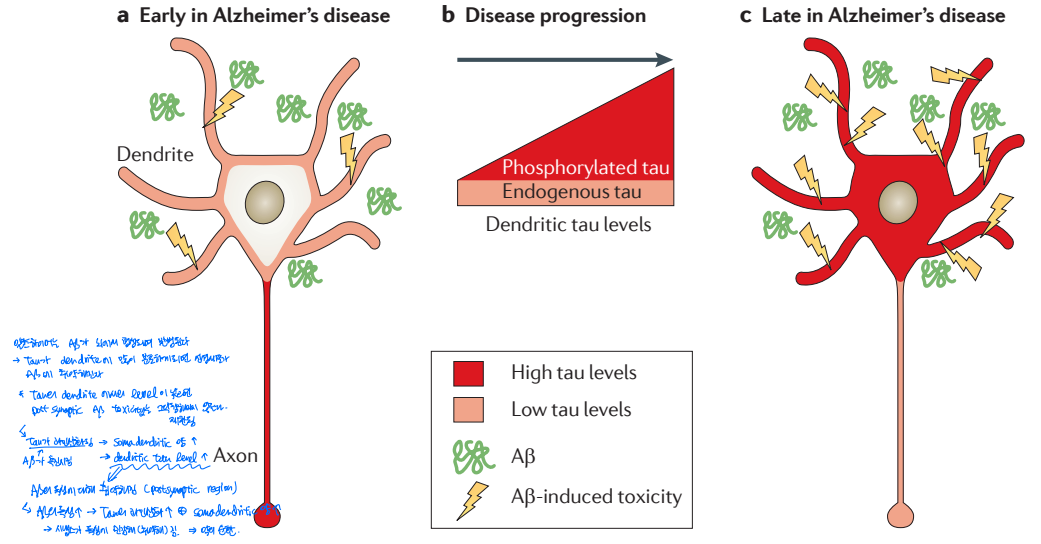

Figure 3 | **Proposed 'tau axis hypothesis' of Alzheimer's disease: progressively increasing levels of dendritic tau make neurons vulnerable to amyloid-β. a** | The onset of Alzheimer's disease (or mild cognitive impairment) is characterized by the initiation of amyloid-β (Aβ) formation in the brain. However, low levels of dendritic tau (in contrast to high axonal levels) are associated with a limited vulnerability of neurons to synaptic (specifically postsynaptic) amyloid-β toxicity. **b** | With disease progression, tau becomes increasingly phosphorylated — a process known to be driven by amyloid-β — and tau accumulates in the somatodendritic compartment of neurons, progressively increasing dendritic tau levels. **c** | In fully manifested Alzheimer's disease, high levels of tau in the dendritic compartment are associated with increased vulnerability of neurons to the toxic effects of amyloid-β at the postsynaptic compartment. As increased amyloid-β toxicity exacerbates tau phosphorylation and its somatodendritic accumulation — thereby sensitizing synapses for amyloid-β toxicity — this may establish a vicious circle.

and/or in other cellular compartments, and that the different tau isoforms may form different complexes. Furthermore, the function of tau at the plasma membrane is not fully understood[28], nor are the mechanisms that determine its association with other proteins and ultimately, its targeting to specific subcellular compartments[25].

Amyloid-β toxicity in cultured neurons is both tau- and FYN-dependent[46,56]. This toxicity has been linked to accumulation of distinct amyloid-β species and concomitant recruitment of tau into lipid rafts[56]. This may suggest that lipid rafts link amyloid-β and tau in distinct membrane compartments *in vivo*. Furthermore, it remains to be established if alterations in FYN have direct effects on tau.

Targeting tau-dependent mechanisms emerges as a suitable strategy in treating diseases with a tau pathology — including Alzheimer's disease[2], in which a combinatorial approach, targeting both tau and amyloid-β, seems prudent. With regard to tau, reducing tau levels or disrupting the NMDAR–PSD95 or the Fyn–Tau interactions are reasonable treatment options[26]. As most evidence suggests that tau needs to be hyperphosphorylated in order to exert toxicity[57], decreasing kinase activities (for example, of glycogen synthase kinase-3)[58,59] or increasing phosphatase activities (for example, of serine/threonine-protein phosphatase 2A)[60], which has shown efficacy in transgenic mouse models of Alzheimer's disease, may be translated into clinical practice. Whether any of these strategies will have side effects in cell types with lower physiological levels of tau — for example, preventing tau-dependent FYN localization in cellular processes in oligodendrocytes affects myelination[61] — remains to be seen.

When Alois Alzheimer revealed the plaques and NFTs under his microscope more than a century ago, one wonders whether he anticipated that the proteins forming these lesions would have such profound roles and be directly linked in the pathogenesis of the disease.

Lars M. Ittner and Jürgen Götz are at the Alzheimer's and Parkinson's Disease Laboratory, Brain and Mind Research Institute, The University of Sydney, Camperdown, 100 Mallett Street, NSW 2050, Australia.
Correspondence to L.M.I. and J.G.
e-mails: lars.ittner@sydney.edu.au; juergen.goetz@sydney.edu.au
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Competing interests statement
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