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Tau Function and Dysfunction in Neurons

Its Role in Neurodegenerative Disorders

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Abstract

Alzheimer's disease (AD) is the most usual neurodegenerative disorder leading to dementia in the aged human population. It is characterized by the presence of two main brain pathological hallmarks: senile plaques and neurofibrillary tangles (NFTs). NFTs are composed of fibrillar polymers of the abnormally phosphorylated cytoskeletal protein tau.

Index Entries: tau; hyperphosphorylated tau; paired helical filaments; neurofibrillary tangles; Alzheimer's disease; tauopathies; transgenic animal models; tau polymerization.

In this review, we summarize the main biochemical characteristics of tau, a protein that in its unmodified form plays a physiological role in stabilizing assembled microtubules. This microtubule-associated protein participates in other pathological states briefly summarized here. The mechanisms for tau polymerization into fibrillar polymers is a subject of active research. We revisit here aspects of the microscopic features of the formation of "paired helical filaments," the product of tau aggregation leading to further proteinaceous aggregates referred to as "neurofibrillary tangles." This review also describes some of the possible transformations experienced by tau proteins in the formation of pathological polymers, including structural changes, phosphorylation by specific kinases, oxidation, glycation, or intersection with other molecules such as glycoaminoglycans. Finally, we summarize the main lessons derived from the generation of single and double transgenic models attempting to reproduce human tau pathology.

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Introduction

Neuron morphology is dependent on the presence of the dynamic assembling-disassembling of a protein scaffold, the cytoskeleton, of which microtubules form an essential component. They play a pivotal role in the formation and maintenance of neuronal processes, i.e., axons and dendrites. Among other factors, the stability of assembled microtubules is enhanced by the presence of a number of microtubule-associated proteins (or MAPs). The tau protein is one such MAPs, participating in the cyclic association-disassociation of microtubules. Indeed, tau proteins are isolated from the in vitro polymerization-depolymerization cycles of microtubules *(1,2)*. Tau protein appears as a series of different polypeptides on electrophoresis gels *(3–5)* (Fig. 1). These different forms are generated by alternative RNA splicing *(6–18)* or by different phosphorylation levels *(5)*. Tau mRNA is transcribed from the tau gene located on chromosome 17 *(19)*, a gene that contains at least 16 exons *(20)*. A GC-rich 5′ untranslated region has been described in the tau gene as a binding region for different transcription factors *(21)*. Recently a tau promoter conferring neuronal specificity has also been described *(22)*.

The expression of different tau isoforms generated by alternative splicing varies in diverse organisms, depending on developmental stage and localization within the nervous system. For instance, tau forms observed in the peripheral nervous system (PNS) are not expressed in the central nervous system (CNS) *(6–8,23–27)* (see scheme in Fig. 1).

The Tau Molecule

Tau isoforms in the CNS have been more thoroughly studied than others. Four different regions have been identified in tau molecules: 1) the amino terminal region, 2) the proline-rich region, 3) the microtubule (tubulin) binding region, and 4) the carboxy terminal region.

The amino terminal region contains acidic sequences and varies in size since it can contain additional exons (exon 2, exon 2 + exon 3); in the case of the PNS, the tau molecule also contains the largest exon (exon 4a). The acidic sequences may be involved in cation binding and an iron-binding-site motif in this region has been proposed *(28)* (Fig. 2). Another motif in the amino terminal region, containing the sequence KKXK, has been suggested to be involved in heparin binding *(28)*. As exons 2 and 3 are not present in every tau isoform, these exons are only alternative spliced in adult brain tissue *(14–18)*.

The tau proline-rich region contains a large number of residues that are potential phosphorylation sites, some of which are followed by a proline residue and also by the motifs PPXXP or PXXP, which are involved in tau interactions with proteins containing SH3 domains. This motif is believed to play a role in the microtubule binding activity of tau *(29,30)*.

The microtubule binding region contains three or four copies of a 31–32 similar (but not identical) repeat *(6–8,16–18)*. These repeats are composed of an 18-residue segment with a highly conserved sequence (known as the "proper" repeats), and a 13–14 residue segment consisting of a less conserved sequence (known as the "inter-repeats"). One of these tubulin binding repeats (the second represented in Fig. 1) is only expressed in adult brain *(9–13)*. In this microtubule binding region the presence of an additional heparin binding site has been suggested *(28)* and a motif present in serpin proteins has been identified. It has been suggested that the tau protein assumes a random coil structure *(3,4)* with a nonglobular tertiary form *(31)*, however, a potential β-pleated region has been proposed for the microtubule binding region *(32)*. Future work should resolve tau structure.

Finally, the carboxy terminal portion of the tau protein also contains a proline-rich region with potential phosphorylation sites, and an acidic region towards the C-terminal end. This C-terminal region also contains a motif (VVSPWNS) similar to that observed in the β-subunit of pyruvate dehydrogenase.

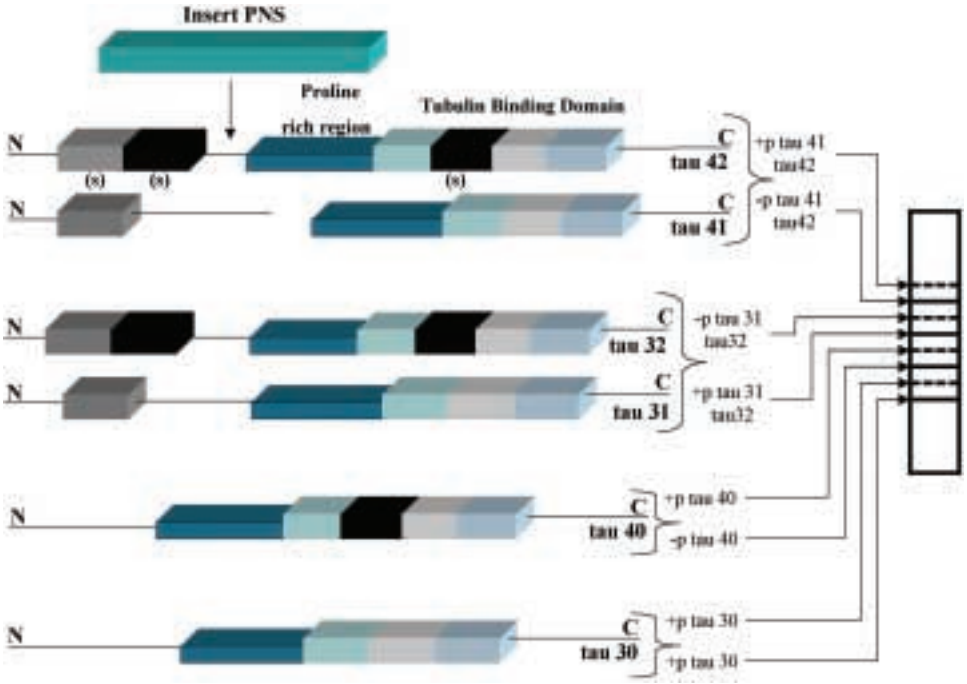

Fig. 1. Tau proteins derive by alternative splicing from a single gene. In peripheral nervous system (PNS) an isoform containing exon 4A is present, while in the central nervous system (CNS) isoforms with exons 2, 3, and 10 are found. These CNS isoforms can be phosphorylated and the modified forms (+p) identified from the non-modified form (–p) by gel electrophoresis (see right side). (s) Indicates exons that could be alternatively spliced.

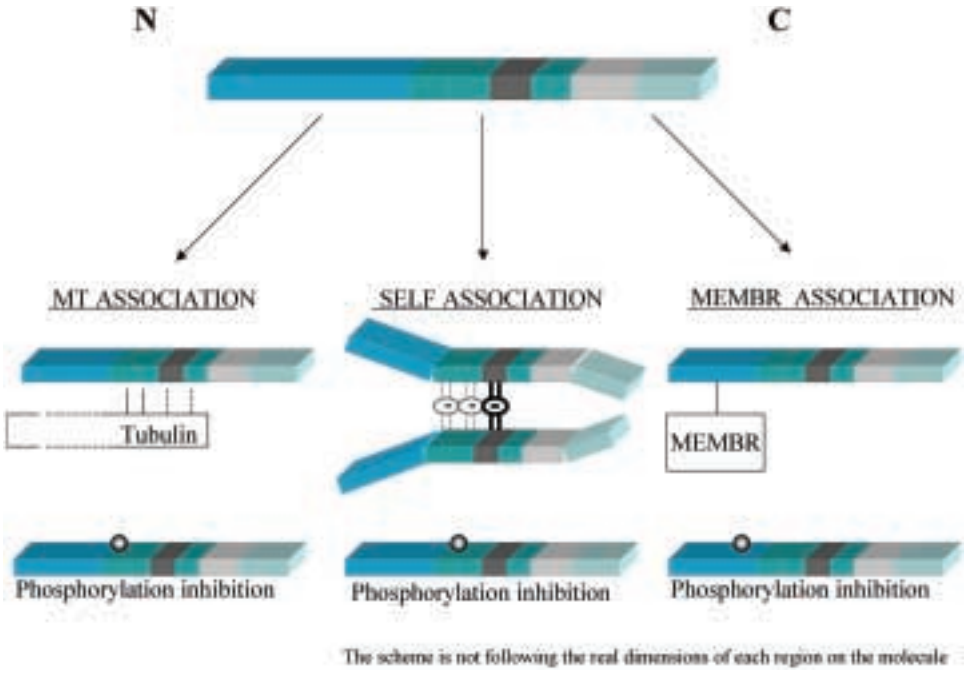

Fig. 2. Phosphorylation of tau protein at specific residues may regulate its interaction with microtubules (left), with itself (center), or with some membrane component (right). See text.

Subcellular Localization of Tau Protein

As expected for a microtubule associated protein, tau has a cytoplasmic localization. However, it has been reported that the tau protein can also bind to plasma membranes through its N-terminal half *(33)* and that the phosphorylation of tau at its proline-rich region prevents such an association *(34)*. This association takes place along the axonal plasma membrane and, particularly, at the growth cones *(35)*.

The reaction of a tau antibody with a nuclear antigen has been proposed *(36)*, but it is as yet unclear if tau has a possible role in the cell nucleus or whether this immunoreactivity is due to a different nuclear protein.

The distribution of tau in mature neurons has been described as being mainly present in the axon *(37,38)*, although a small proportion might be present in the somatodendritic compartment *(39)*. As indicated earlier, a proportion of tau could be associated with the microtubules, with another proportion associated with cell membranes.

Tau Interacting Proteins

Besides tubulin, tau proteins can bind to many other proteins such as spectrin *(40)* or protein phosphatase 1 (PP1). Other tau interacting proteins have been reported to bind to the tau molecule through its microtubule binding region. They include protein phosphatase 1 *(41,42)*, protein kinase CDK5 *(43)*, presenilin 1 *(44)*, or α-synuclein *(45)*. A number of proteins interacting with the tau molecule through its proline-rich region have also been reported. Among these are phospholipase C-8 *(46)*, a protein with a SH3 domain that could bind to the PPXXP tau motif *(47)*; fyn, a tyrosine kinase also containing a SH3 domain *(48,49)*; and actin *(50)*. In these latter cases, the protein interactions with tau are suspected to enhance its association with cell membranes. Preliminary studies applying the two-hybrid method have indicated the existence of other cell membrane associated proteins capable of binding to the tau protein through the proline-rich region (Hoenicka et al., unpublished results).

Recently, some attention has been paid to prolyl isomerase-1 (PIN-1), a chaperon protein that binds to phosphoproteins containing phosphoserine or threonine followed by proline. Tau is thus a likely substrate that could interact with PIN-1 via its proline-rich region *(51)*.

Tau Protein Modifications

As indicated earlier, some kinases and phosphatases modulate the degree and pattern of the tau molecule's phosphorylation. Since the pioneer work of Grundke-Iqbal et al. (1986), it has been widely accepted that tau is a phosphoprotein that can be modified by many different protein kinases, such as proline-directed protein kinases (PDPK) like GSK3 or cdk5, also known as tau kinase I and II *(52)*; nonproline directed protein kinases, like pKA *(53,54)*; MARK kinase *(55)*; or PKC *(56)*. Also, phosphorylation by MAP kinases has been suggested *(57)*. Furthermore, MAP-kinases are upregulated in cells lines over-expressing wild-type amyloid precursor protein (APP) generating increased levels of intracellular A-β peptides *(58,59)*. Phosphorylation by PDPK, mainly takes place at the proline-rich and C-terminal regions in flanking sequences to the tau microtubule binding region, whereas phosphorylation by non-PDPK may occur at the tau microtubule-binding region. Phosphorylation by other types of kinases, such as CKII, has also been reported at the amino-terminal region *(56,60)*.

The modification of tau by kinases such as GSK3, PKA, or MARK, appears to decrease the affinity of tau protein for the microtubules *(55,61–66)*. In addition, phosphorylation due to PDPK activity could favor dimerization of tau proteins *(5,67)*.

In summary, phosphorylation of tau at different sites could affect not only its interaction with microtubules, but also its capacity to aggregate or interact with other proteins (Fig. 2). Additionally, the balance of kinases and phosphatases could result in tau isoforms with different levels of phosphorylation. These differences could not only regulate microtubule binding, but also the cell localization of tau, and therefore its association to membranes

(33,34), to nuclei *(36)*, or its transport to diverse localizations within neurons *(39)*.

From the pathological point of view (see below), differences in the aggregation of different phosphorylated tau isoforms have been reported *(68)*. A more descriptive role for tau phosphorylation can be found in a recent and extensive review *(69)*.

Tau Function

The search for factors affecting microtubule assembly led to the discovery of tau as an important microtubule-associated protein *(1,2)*. Indeed, it has been shown that tau promotes microtubule polymerization in vitro *(70,71)* and can supress microtubule dynamics, stabilizing the assembled microtubules *(72)*. Applying tissue-culture techniques, a role for tau has been also suggested in microtubule stabilization and neuritogenesis *(73–75)*. However, in contrast with the aforementioned results, a tau-deficient mouse produced by gene targeting has been shown to be viable and not very different from tau-containing mice *(76)*, beyond a decrease in the number of microtubules in small caliber axons, and some behavioral deficits *(77)*. To explain this apparent paradox it has been suggested that other microtubule-associated proteins, such as MAPIA, are increased in tau-deficient mice, as a developmental compensatory phenomenon *(76)*. In this regard, defects in axonal elongation have only been found in mice that have simultaneously disrupted tau and MAPIB genes *(78)*.

Tau in Pathological Processes

Tau proteins form aberrant aggregates in some neurological disorders such as Alzheimer's disease (AD) and the more recently described group of diseases referred to as tauopathies. In AD, there are two main pathological structures present in the brains of patients: senile plaques and neurofibrillary tangles (NFTs) *(79–83)*. The key protein responsible for the generation of plaques is the amyloid precursor protein (APP), a fragment of which (Aβ peptide) is neurotoxic and tends to aggregate in pleated structures. On the other hand, NFTs are composed of paired helical filaments (PHF) *(84)*, which are polymers of abnormally phosphorylated tau *(85–96)*. It is the aggregation of PHFs that leads to the formation of NFTs, intracellular pathological fibrillar structures visible in light microscopy (*see* Fig 3). The number of NFTs has been correlated with the level of dementia *(97,98)*. Therefore, tau pathology might be the key to deficits in higher CNS functions observed in AD. The monoclonal antibody (MAB) coded 6.423 has been shown to recognize fragments of tau forming the "core" of PHFs in AD brains *(91)* while the MAB Alz 50 *(99)* has been recently characterized as binding to a folded conformation of tau *(100)*. The comparative analysis of bindings sites in a large series of aged controls and AD brains has shown that there is a clear correlation between the number of sites (PHFs) immunoreactive to the 6.423 MAB and the duration of the dementia *(101)* while the Alz 50 sites appeared earlier and more ubiquitously (NFTs and non-NFT structures).

This appearance of conformational changes in tau as early alterations in AD neuropathology has been eloquently confirmed in a recent study *(102)*. It is interesting to note that, with the 6.423 mab (PHFs-core), tau fragments apparently aggregate first in the perinuclear cytoplasm of neurons in a diffuse manner before presenting themselves as part of the intracellular NFTs *(101)*. Such diffuse, perinuclear aggregation of tau-hyperphosphorylated material resembles the effects on hippocampal tau after the transgenic postnatal expression of GSK3 *(103)* (see below animal models section). Also, it should be kept in mind that this tau conformational change, and later aggregation into PHFs and NTFs, might very well have a CNS topographic evolution in human AD pathology besides the macromolecular time-dependent changes. Thus, Braak and Braak have most elegantly shown the successive accumulation of NFTs in the AD brain in a stage-wise fashion, commencing from layer 2

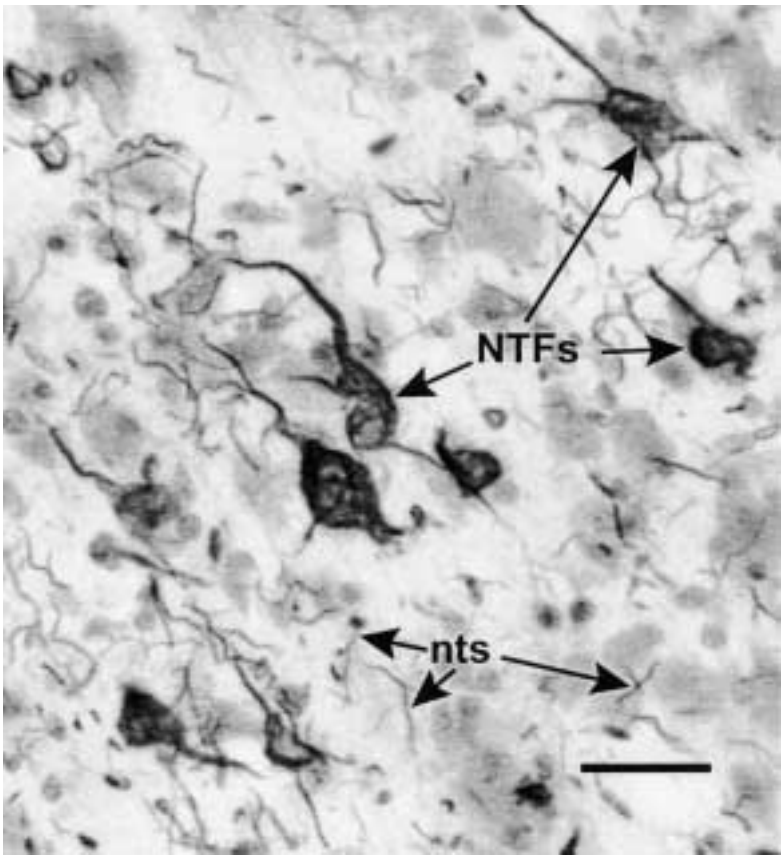

Fig. 3. The presence of pathological, abnormally phosphorylated tau is evident in AD in the form of neurofibrillary tangles (NFTs) within neuronal cell bodies and proximal dendrites as well as in neural processes, as "neuritic threads" (nts), within the neuropil. The immunoreaction illustrated is directed against microtubule binding domain of tau forming the core of paired helical filaments (PHFs) (mab 6.423). Micrograph from frontal cortex of an Alzheimer's patient with advanced dementia. The section was counterstained with toluidine blue. Unpublished micrograph from the study by Mena et al. *(101).* Scale bar 25 microns.

and 4 of the entorhinal cortex *(83).* In AD, tau pathology has been correlated with phosphorylation of the protein, a lack of binding to microtubules, and the formation of NFTs *(104).* All of these aspects have thus been studied to some extent.

In AD postmortem material, tau phosphorylation has been found to principally increase (but not exclusively so) at sites modified by PDPK enzymes such as GSK3 *(105).* In consequence, this type of modification has been extensively studied (e.g., *see* [106]). More recently, studies on the regulation of kinases (like GSK3 or PKA) or phosphatases (like PP2A) that could affect the final level of phosphorylation of the tau molecule have been undertaken. In this way the involvement of factors like wnt *(107,108),* insulin, or insulin-like growth factor (IGF-1) in the regulation of tau phosphorylation by GSK3 has been discovered. As a result, the application of specific inhibitors of GSK3, such as lithium, has been found to have an impact on the pattern of tau phosphorylation in neuroblastoma cells *(62).* The regulation of tau PDKF phosphorylation sites by the activation of muscarinic

acetylchorine receptors in PC12 cells has been described *(109,110)*. Also, the possible effect of an increase of cAMP in the regulation of tau phosphorylation at PDPK sites has been raised *(111)*. However, recently, it has been indicated that PKA could inhibit GSK3 activity *(112)*. Thus, it is difficult to explain the observation that single tau molecules can be hyper-phosphorylated simultaneously in both GSK3 and PKA sites, unless there is a mechanism in AD that causes this. This point requires further analysis.

One result of the phosphorylation of tau at different sites is a conformational change of the molecule that can be reversed by the presence of trimethylamine N-oxide (TMAO), a natural occurring osmolyte. Tau phosphorylated by GSK3 in the presence of TMAO is able to promote tubulin assembly *(113)*. Most interestingly, a conformational reversion of tau has been demonstrated in the presence of the chaperon protein Pin-1 *(51)*, a molecule that binds to the phosphothreonine-proline motif and that seems to facilitate the posterior action of PP2A on this phosphothreonine, implying therapeutic opportunities if tau phosphorylation becomes a target *(114)*.

The level of tau phosphorylation could, obviously, also be regulated by phosphatases. Studies indicate that PP2A is the major brain enzyme that dephosphorylates tau proteins that have been phosphorylated at PDPK or PKA sites *(115–120)*. Thus, the regulation of phosphatases is becoming an issue of interest in tau biology. For example, it has been shown recently that the function of PP2A appears to be modified by its carboxylmethylation *(121)*. The spectrum of PP2A appears to be wider than initially suspected, as there are indications that it acts on phosphorylated GSK3 *(122)*.

Hyperphosphorylation of tau could affect the molecule in several ways, as has been highlighted by the higher proteolytic resistance of hyperphorylated tau residues *(123,124)*. As will be discussed later, changes in the phosphorylation state of tau occur not only in AD, but also in other neurological disorders such as the "tauopathies" resulting from cerebral ischemia *(125)*, apoptosis *(126)*, and cellular stress *(127)*. Additionally, some of the kinases involved in tau phosphorylation, such as GSK3, could also affect some elements involved in proteosome degradation *(128)*, which could result in the abortive degradation of tau *(129)*.

Another feature of tau pathology in AD is the decrease in its binding to microtubules, which thus affects microtubule-cytoskeleton stabilization *(130)*. In this regard, the work of Iqbal and collaborators *(131)*, indicating that phosphorylated tau might sequester other MAPs, has been of great importance, as this action would facilitate the breakdown of the microtubule network. This possible change in microtubule organization could affect other subcellular structures such as the mitochondria *(132)* or lysosomes *(133)*, and alterations of these cellular organelles could promote further tau pathology *(134)*. The involvement of lysosomes in tau neuropathology could be of particular relevance since modifications in these organelles appear to precede the overt AD neuropathology *(133)*. Also, it has been suggested that tau phosphorylation could affect axonal transport *(135)*, an effect that could be deleterious to neuronal function and the reason for synaptic loss, a key factor in unleashing the clinical consequences of AD *(136)*.

Tauopathies

It has been known for some time that NFTs are a prominent feature of the CNS neuropathology of a number of neural disorders other than AD. More recently it has become evident that tau is present in all of these NFTs in aggregated forms and with a high phosphorylation level. These disorders are today known as tauopathies. Among the tauopathies are dementias such as progressive supranuclear palsy (PSP), Pick's disease (PiD), corticobasal degeneration (CBD), or frontotemporal dementia with Parkinsonism, linked to chromosome 17 (FTDP17). For a more exhaustive description of these tauopathies and their genetic background, see Spillantini

and Goedert *(137)*, Schmidt and collaborators *(138)*, and Lee and collaborators *(139)*. These tauopathies exhibit some differences in their molecular and pathological features, e.g., the affected CNS region, the characteristics of the assembled filaments, and the type of tau isoforms forming the filaments *(140)*.

One of the most studied tauopathies has been FTDP17, since in this disorder the onset of the disease correlates with mutations on the tau gene. Mutations at introns and exons have been described. The mutations occurring in exons are preferentially present in the microtubule-binding region leading to interference of function *(141,142)* in the binding sites of PP2A to tau protein *(143)*, and in self-assembling regions of the tau protein (see below).

Additionally, silent or intronic tau mutations have been reported in FTDP17. These mutations affect nuclear RNA processing and lead to an increase in the expression of exon 10 *(144–149)*. Furthermore, it has been recently reported that the regulation of the alternative splicing of exon 10 is mediated through the phosphorylation of a splicing factor *(150)*.

Animal Models

A number of mouse transgenic models have been developed in recent years with the objective of reproducing aspects of the tau pathology as found in AD and in tauopathies. Thus, with the overexpression of transgenes coding for the shortest human tau isoforms, "pretangle" tau pathology has been reported *(151,152)*. An analogous accumulation of hyperphosphorylated tau in a somatodendritic compartmentalization in hippocampal neurons has been recently observed in a mouse transgenic model overexpressing the tau-phosphorylating enzyme GSK3, with the conditional expression of the transgene after the development of the CNS *(103)*.

In some transgenic models, tau aggregates and spheroidal inclusions have been observed, principally in neurons with long axons such as spinal motor neurons, when a high level of the shorter or longer human tau isoforms transgenes is expressed *(153)*. The overexpression of longer forms has led to phenotypes with severe motor axonopathy and amyotrophy, but no tangle formation *(154)*. The pathological fibrillar phenotype resulting from tau overexpression is, so far, more prominent in spinal motoneurons, although abnormally phosphorylated tau is also found in cortical areas. The resulting axonopathies and the accumulation of congophilic neurofibrillary material in some transgenic lines appears to be an age-dependent phenomenon *(153)*. Although in most cases no AD-like PHFs structures have been observed, recently, with the transgenic expression of some tau isoforms bearing mutations present in FTDP17, aggregated tau filaments resembling AD and tauopathy-like fibrillar structures have been reported *(155,156)*. Furthermore, the presence of bona-fide tau filaments in a transgenic mouse overexpressing a tau isoform containing three of the FTPDP17 mutations has been observed *(157)*. Two of these mutations are present in the microtubule tubulin region, while the third is localized at the C-terminal region, thus affecting the corresponding phosphorylation targets in that molecular domain.

A very exciting development is the possibility of linking Aβ pathology with tau pathology, as both are characteristically present in AD. Two recent communications applying tau transgenic models provide clues for a direct relationship between amyloidogenesis and tangle formation. In both reports, transgenic lines express the P301L tau mutant protein. In one of these reports, the incidence of tangle-like structures was enhanced in the limbic system by crossing the P302L line with a transgenic mouse line expressing the Swedish double mutation of APP *(158)*. In the other report, the application of the Aβ 42 peptide in the somatosensory cortex induced the formation of NFTs in the amygdala of P301L tau transgenic mice *(159)*. These reports would suggest that extracellular Aβ fragments would trigger mechanisms leading to NFT formations, yet unknown.

These mouse models are of obvious potential value in experimental therapeutics. Further-

more, it is expected that they will be extended to other species, such as the rat, which has a richer behavioral display than the mouse. For a recent and comprehensive review of transgenic animal models of the tau pathology, see Gotz *(160)*.

Tau Polymerization in Vitro

Tau polymerization into fibrillar structures has been observed in vitro. As early as 1986, Montejo and collaborators described purified tau protein being polymerized into filaments *(161,162)* and molecular modifications, such as deamination, facilitating this polymerization of tau. Tau assembly in vitro was further confirmed by the same group *(163,164)* and by other groups using recombinant tau *(165,166)*. It was later shown that deamidation and isoaspartate formation occurs in tau forming PHFs *(167)*.

A relatively high protein concentration is apparently needed for tau polymerization. In consequence, factors that could facilitate tau polymerization at lower protein concentrations have been investigated. Among them, molecules such as sulfoglycosaminoglycans (sGAG) that are present in NFTs *(168)* have been tested using recombinant tau. The sGAG molecules enhance the rate of tau assembly in vitro *(169)*, a result that was further confirmed using phosphorylated forms of tau as the substrate *(170,171)*. Afterwards, it was found that other polyanions can also facilitate tau polymerization *(172)*. Additionally, it was found that sGAG, or other polyanions like the glutamate-rich peptide located at the C-terminal region of tubulin, could increase GSK3 phosphorylation of tau *(161,173)*, perhaps resulting in a conformational change of tau protein that could be similar to that needed for tau aggregation. Studies with the sGAG-induced tau polymerization have also revealed that the smallest tau region able to aggregate is present in the third tubulin-binding motif *(169)*, a region differing from that principally involved in microtubule-binding function *(104)*, which is located in the first two tubulin-binding motifs. Furthermore, a role in the induction of PHF helicity by sGAG has been proposed *(28)*. Finally, the presence of mutations like those reported for FTDP-17 could favor tau aggregation in the presence of sGAG *(174)*.

Other factors can apparently contribute to tau assembly. Thus, tau can be assembled through oxidation processes involving iron *(175)*, and it has been suggested that ferritin could be the source for iron in a redox reaction leading to tau assembly in PSP, a well-established tauopathy *(176,177)*. Fatty acids have also been shown to induce tau polymerization in in vitro models *(178–180)*. Other modifications like truncation *(132,181)* have been suggested to play a role in facilitating tau assembly. In fact, truncated forms of tau ultimately constitute the "core" of PHFs *(132)*. Finally, it has been shown that the aggregation of PHF-like tau filaments into NFT-like bundles could occur through another tau modification, glycation *(182,183)*.

Until recently *(184)*, it has not been possible to establish a correlation between the two tau changes, phosphorylation and tau aggregation, observed in the AD brain. Perez and collaborators *(185)* have suggested that highly phosphorylated tau—but not unmodified tau—can be assembled at low protein concentrations in the presence of hydroxynonenal, a natural oxidation product of the fatty acid metabolism.

A summary of the possible mechanism for tau assembly into NFT is indicated in Fig. 4.

Final Remarks

While tau is apparently a dispensable microtubule-associated protein, its presence in the CNS in a modified form can have profound pathological effects upon neurons. The toxic effects of tau are seemingly the result of a gain of function, and since a variety of factors might be involved in tau modification, alteration in the levels of functions of these factors could promote tau pathology. In this context the abnormal phosphorylation of tau is central to its pathology. In consequence, factors regulating tau kinases or phosphatases could lead to

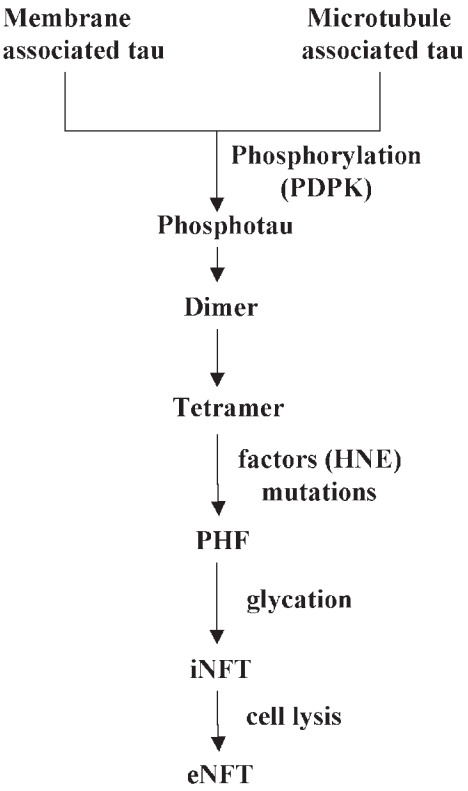

Fig. 4. A model for tau assembly into intracellular (i) or extracellular (e) neurofibrillary tangles (NFT) (see text).

tau aggregation and sequestering of other MAPs, resulting in a disorganization of the microtubule network, promoting the formation of PHFs and, in turn, NFTs.

It is thought that tau aggregation plays a key role in the deleterious effects of this protein in neurodegeneration. In this process, factors like sGAG might be involved. However, the possible physiological relevance of sGAG in inducing tau polymerization remains unclear. It has also been suggested that tau could be cleaved by lysosomal enzymes. If such an interaction of tau with the endosomal-lysosomal compartment is confirmed, then it is possible that sGAG-induced-tau polymerization could have a physiological meaning.

Finally it is abundantly clear that phosphorylated tau—but not unmodified tau—can be assembled in the presence of lipid peroxidation products. Therefore, oxidative stress could contribute significantly to the generation of tau modifications that facilitate pathological tau aggregation.

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