Neurofibrillary Tangles and Alzheimer's Disease

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Abstract
The neuropathological diagnosis of Alzheimer's disease relies on the presence of both neurofibrillary tangles and senile plaques. The number of neurofibrillary tangles is tightly linked to the degree of dementia, suggesting that the formation of neurofibrillary tangles more directly correlates with neuronal dysfunction. The regional pattern of areas affected by neurofibrillary tangles formation during the course of the disease is relatively stereotyped. Neurofibrillary tangles are composed of highly phosphorylated forms of the microtubule-associated protein tau. Phosphorylated tau proteins accumulate early in neurons, even before formation of neurofibrillary tangles, suggesting that an imbalance between the activities of protein kinases and phosphatases acting on tau is an early phenomenon. The latter might be related to changes in signalling through transduction cascades, since many of the protein kinases generating phosphorylated tau species participate in signalling pathways. The accumulation of neurofibrillary tangles and phosphorylated tau species is associated with disturbances of the microtubule network and, as a consequence of the latter, of axoplasmic flows. The mechanistic relationship between the formation of neurofibrillary tangles and senile plaques is still little understood and in vivo formation of neurofibrilllary tangles in experimental models has not yet been achieved. Future animal models, e.g. transgenic animals expressing combined key human proteins, will hopefully reproduce faithfully all the major cellular lesions of the disease.

Introduction

Alzheimer's disease is the most frequent cause of dementing condition and its prevalence increases exponentially with age, from 0.3% for the age group 60–69 to 10.8% for the age group 80–89 in European countries [1]. The genetic analysis of Alzheimer's disease has made major progress in the recent past. Familial Alzheimer's disease, an autosomal dominant condition, has been estimated to represent up to 10% of all Alzheimer disease cases. Mutations of the presenilin 1 and 2 genes and of the amyloid peptide precursor gene probably account for 65–75% or familial cases [2]. The ε4 allele of apolipoprotein E is now known to be a susceptibility gene for both familial and sporadic cases of Alzheimer's disease [3].

The characteristic neuropathologcal lesions of the disease, senile plaques and neurofibrillary tangles (NFT), are present in sporadic cases as well as in the familial forms due to various mutations, indicating that they constitute a kind of 'final common pathway' responsible for the clinical expression of the disease. Particularly, the formation of NFT is thought to be closely linked to neuronal dysfunction and dementia. The study of the molecular composition and mechanisms of formation of NFT is thus believed to be essential for our understanding of the pathogenesis of Alzheimer's disease. This paper is devoted to a general review of the structural and molecular characteristics of NFT and how the pathogenesis of this lesion and its effects on neuronal function are presently understood.

The Neuropathological Lesions of Alzheimer's Disease

Neurofibrillary Tangles

NFT are composed of bundles of abnormal filaments accumulating in neuronal perikarya, dendrites, and axons (fig. 1). Ultrastructurally, these filaments show regular constrictions or appear straight and have been described

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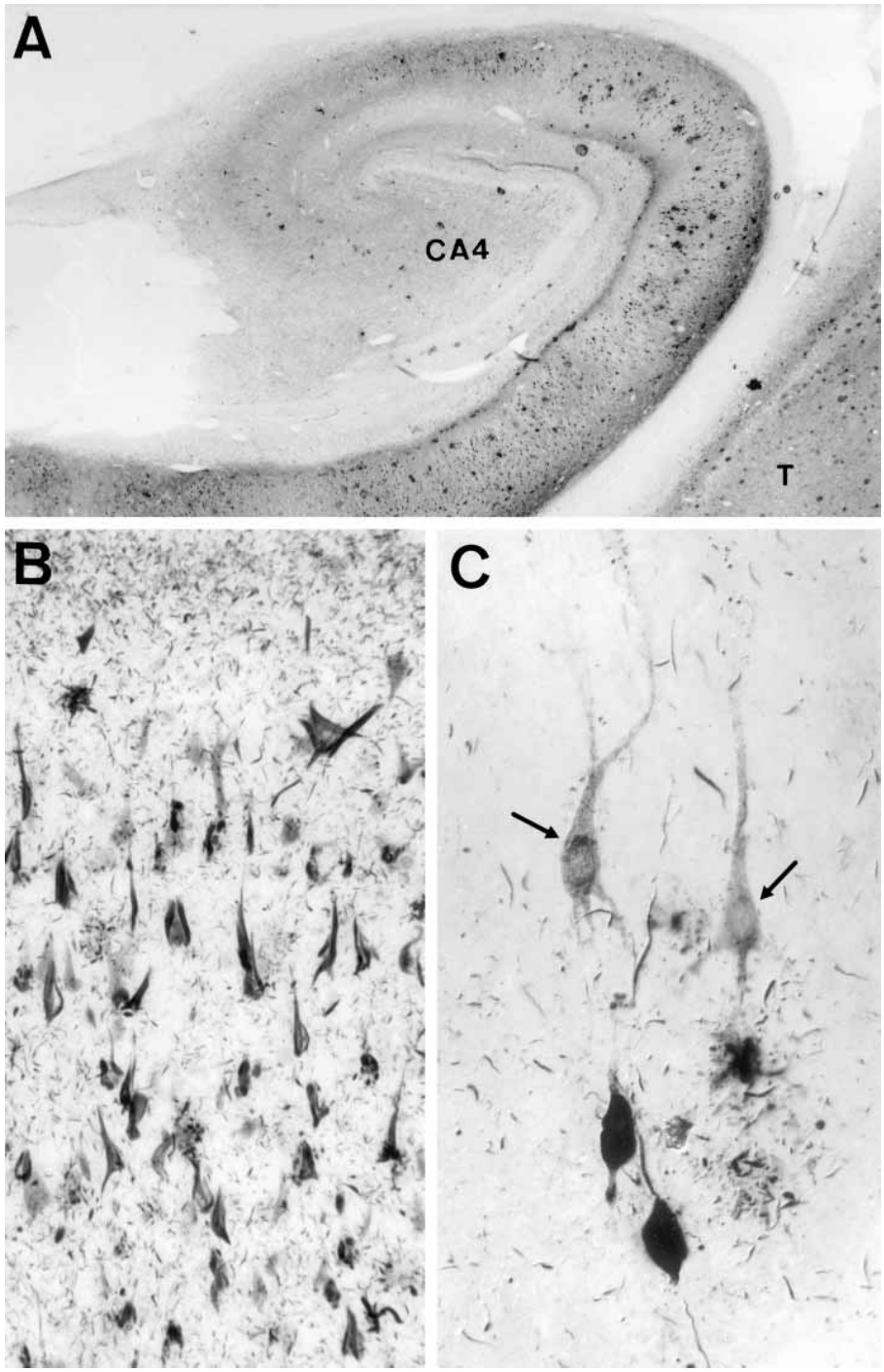

Fig. 1. Immunolabelling with an antitau antibody (no counterstaining) on tissue sections of the hippocampus of a patient with Alzheimer's disease. **A** The strong labelling is due to the detection of abnormal PHF-tau proteins associated with NFT, dystrophic neurites of senile plaques, and neuropil threads. In this advanced case, NFT are abundant in the Ammon's horn, the subicular areas, and the temporal neocortex (T). Some regions, e.g. the CA4 sector of the Ammon's horn, are relatively spared. **B** CA1 sector. Numerous neurofibrillary tangles are detected. Many fill the neuronal perikarya and extend into apical dendrites. The neuropil is crippled with small tau-immunoreactive neurites (neuropil threads). **C** Two strongly tau-immunoreactive NFT are adjacent to two neurones exhibiting a fainter and granular tau immunoreactivity in their perikarya and dendrites ('pretangle' stage, arrows). **A** × 12. **B** × 180. **C** × 360.

as two filaments helicoidally twisted around each other (hence their name 'paired helical filaments', PHF) (fig. 2) [4]. Further studies have shown that a PHF closely resembles a twisted ribbon [5, 6] whereas cross-sections of its core show two C-shaped units [7]. Neuropil threads are composed of small curly, dystrophic neurites dispersed in the neuropil (fig. 1B, C) and containing abnormal filaments.

NFT are classically identified with silver staining methods but are also demonstrated by their green bire-

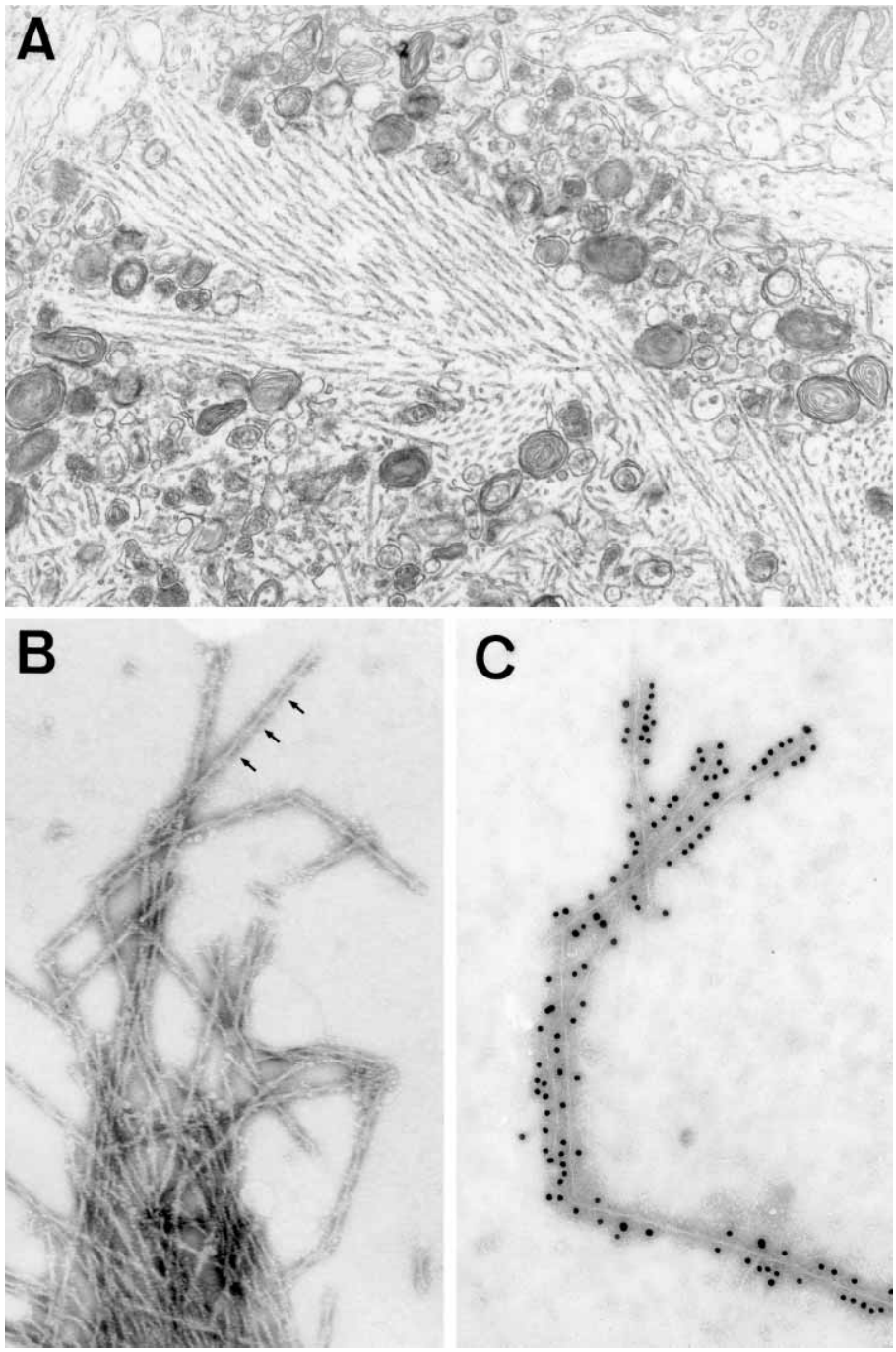

Fig. 2. Transmission electron microscopy. **A** Ultrathin tissue section (frontal cortex). Numerous paired helical filaments are present in the cytoplasm of this neurone. They are admixed with accumulations of vesicular organelles. **B, C** PHF isolated from brain tissue (negative staining). The regular constrictions (arrows) are well visible. These PHF are labelled with an anti-tau antibody in **C**. A secondary antibody conjugated to gold particles (black spheres) was used to detect the antitau antibody. **A** ×25,500. **B, C** ×53,000.

fringence after Congo red staining and by fluorescence after thioflavine S staining [8]. Immunocytochemical labelling with antibodies to tau proteins, the main component of PHF (see below), is a robust reproducible method for the detection of neurofibrillary lesions, at least as sensitive as silver staining [9, 10].

Several morphological types of NFT can be distinguished, most probably corresponding to different evolutionary stages. 'Pretangle' stage is characterized by the accumulation of phosphorylated tau in the somatodendritic compartment, without formation of PHF [11, 12]. At a following stage, a few tau-immunoreactive rods

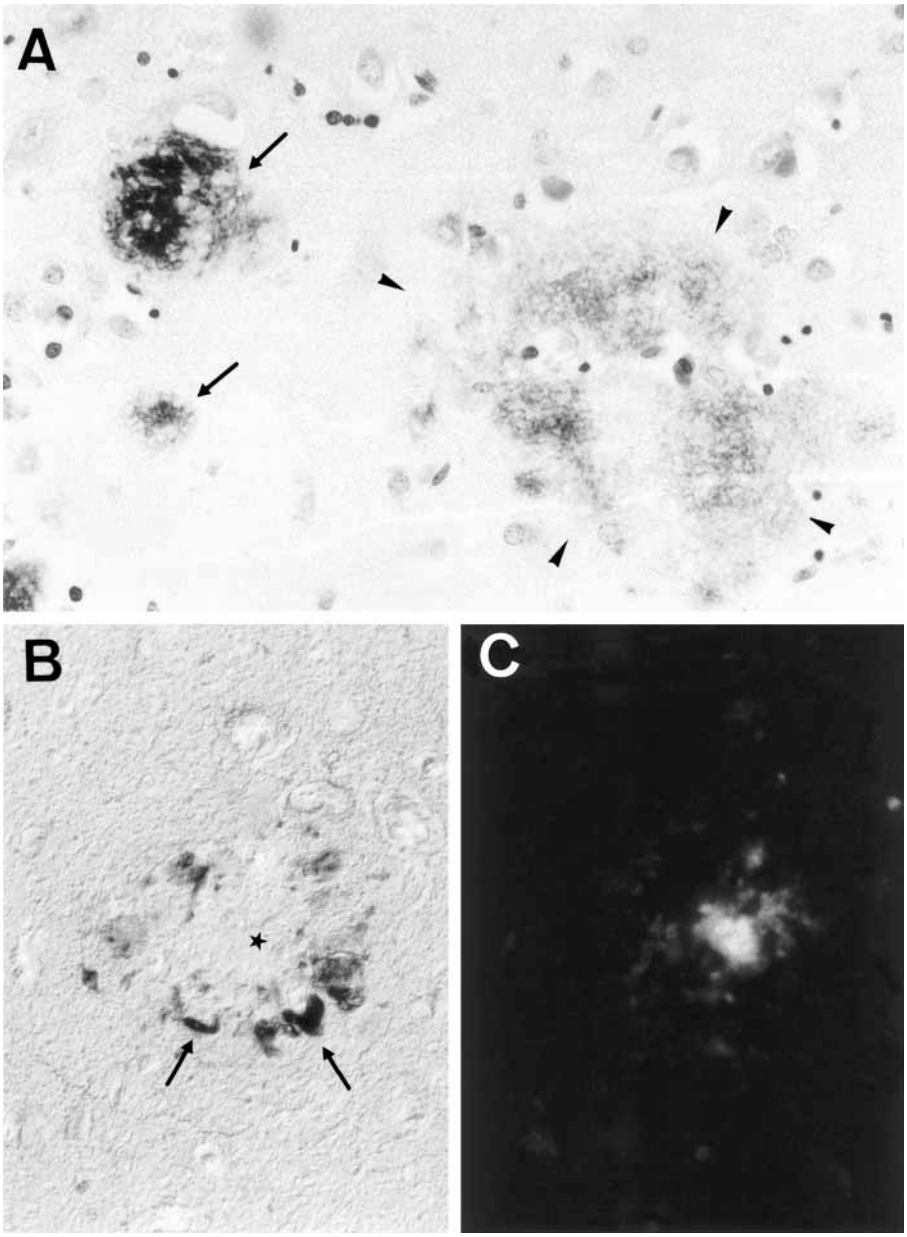

Fig. 3. Tissue sections of the hippocampus in an Alzheimer's disease patient. **A** Immunolabelling with an anti-Aβ amyloid antibody. Two senile plaques with fibrillar Aβ amyloid core (arrows) are adjacent to a larger diffuse plaque (arrowheads), containing non-fibrillar Aβ amyloid. **B, C** Double immunolabelling with an anti-tau antibody (**B**) and an anti-Aβ amyloid antibody (**C**). This senile plaque shows tau-immunoreactive dystrophic neurites (arrows) surrounding an amyloid core (asterisk), labelled by the Aβ amyloid antibody, as shown in **C**. **A** ×290. **B, C** ×460.

appear in soma and dendrites. They are also detected by silver staining and correspond to early NFT and neuropil threads. Classical NFT are made of tightly packed bundles filling a more or less important part of the cell body and extending into dendrites. Neuronal death is accompanied by a partial desaggregation of NFT, exhibiting a more loose aspect. Extracellular tangles, which reflect neuronal loss [13], persist seemingly for a long period presumably as a result of their partial resistance to proteolysis, although they lack the N-terminal domain of tau [14, 15].

Senile Plaques

The senile plaques are composed of an extracellular deposit of amyloid fibrils surrounded by a neuritic crown of dystrophic neurites (fig. 3). Some of these neurites contain PHF and are labelled by anti-tau antibodies (fig. 3B). Only a proportion of plaques shows these tau-immunoreactive neurites, this proportion being more important in the most demented patients [16, 17]. The amyloid fibrils are composed of the Aβ amyloid peptide (Aβ), a 39–43 amino acids peptide deriving by proteolysis from the larg-

er amyloid peptide percursor (APP) [18]. Deposits of Aβ are also observed in the walls of cerebral vessels (amyloid angiopathy) and in the form of nonfibrillar deposits in the neuropil (diffuse plaques), considered as early stages of senile plaques (fig. 3A). A detailed account of other molecular and cellular components of senile plaques can be found in some recent reviews [19].

Other Lesions

A neuronal loss has been well documented in Alzheimer's disease and is correlated with the number of NFT but might outnumber it [20]. A synaptic loss also occurs and is correlated with the number of NFT (much less with the number of senile plaques) but shows an independent correlation with the degree of dementia [21]. Cortical Lewy bodies, granulovacuolar degeneration and Hirano bodies are neuronal lesions often encountered, but a close relationship between them and the development of NFT has not been established.

Neurofibrillary Tangles and the Diagnosis of Alzheimer's Disease

Neuropathological Criteria in Alzheimer's Disease

Quantitative neuropathological criteria, mainly based only on the density of senile plaques, have been proposed [22, 23]. However, in many anatomoclinical studies the densities of NFT were found to be more tightly linked to the degree of dementia than senile plaques [9, 10, 16, 24], indicating that the formation of NFT more directly correlates with neuronal dysfunction. Recent consensus recommendations for the postmortem diagnosis of Alzheimer's disease take into account semiquantitative estimates of both NFT and senile plaques and their topography [25].

The regional pattern of areas affected by NFT formation during the course of Alzheimer's disease is relatively stereotyped and a hierarchical order of areas involvement has been found [26–29], leading some authors to propose a neuropathological stageing in 6 stages [27]. NFT are first found in the transentorhinal cortex, a transition area between the adjacent entorhinal cortex and the temporal neocortex (stage I); NFT appear then in layer pre-α of entorhinal cortex (stage II); at these stages, patients do not exhibit any cognitive deficit. At following stages (III and IV), NFT become abundant in the entorhinal cortex and numerous in hippocampus; these stages correspond to clinically incipient Alzheimer's disease. At the final stages (V and VI), NFT are abundant in neocortical association areas (where they are predominantly found in layers III and V) and this stage corresponds to full-blown Alzheimer's disease. Several brain areas are relatively spared, such as primary motor and sensory cortical areas, cerebellum, and spinal cord. Some neuronal populations seem resistant to the formation of NFT [30, 31]. The molecular reason underlying this relative specificity in the spreading of NFT remains a still unresolved question in Alzheimer's disease.

The distribution and spreading of senile plaque and diffuse plaques follows a different and much more variable pattern. They are generally first found in isocortical areas of frontal, temporal and occipital lobes [27, 29].

Neurofibrillary Tangles in Other Diseases

Athough Alzheimer's disease is by far the most common pathological condition in which NFT are found, NFT or NFT-like inclusions are also encountered during normal aging and in some other neurological diseases, including Down's syndrome, dementia pugilistica, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, Niemann-Pick disease, type C, subacute sclerosing panencephalitis [32, 33]. However, abundant NFT are not observed in cognitively unimpaired individuals, in contrast with Aβ deposits, which can be abundant in nondemented people [34]. Neurofibrillary lesions have also been described in oligodendrocytes and in astrocytes, e.g. in progressive supranuclear palsy and in multiple system atrophy. All NFT in these conditions share a tau immunoreactivity, but they can be composed of different types of tau isoforms and show ultrastructural differences [35]. For instance, paired helical filaments are observed in Down's syndrome and dementia pugilistica, and straight filaments in progressive supranuclear palsy and corticobasal degeneration.

Strikingly, the development of abundant NFT is a process mainly restricted to the humans. Occasional NFT have been described in some species, e.g. in aged sheep [36]. On the contrary, senile plaques are frequently observed in several species of aged mammals, e.g. in aged dogs [37].

Tau in CSF

The concentration of tau proteins, on average, is increased in the cerebrospinal fluid of Alzheimer disease patients when compared with nondemented controls [38, 39], including in mildly demented patients [40]. Elevated tau in the cerebrospinal fluid has been observed occasionally in other neurological conditions, which can however often be distinguished from Alzheimer's disease on clinical grounds.

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Tau Proteins

Tau proteins were originally discovered as factors copolymerizing with microtubules and promoting their assembly [41]. Microtubules are one of the fiber systems (with microfilaments and neurofilaments) composing the neuronal cytoskeleton. Microtubules are essential for the maintenance of the shape of the neuron and play a fundamental role in the axoplasmic transport of various molecules and organelles. In neurons, microtubules are composed of the globular α- and β-tubulin proteins, and of a set of microtubule-associated proteins (e.g. MAP1a, b, MAP2, and tau proteins). In adult human brain, tau exists as a set of six isoforms ranging from 352 to 441 amino acids (fig. 4) [42] generated by alternative splicing of a single mRNA, transcribed from a gene localized on chromosome 17. A specific tau isoform has been identified in the peripheral nervous system [43]. Tau is abundantly expressed in neurons but is also expressed in oligodendrocytes and astrocytes. In developing neurons tau is present in the whole cell [44]. In mature neurons, it is concentrated in axons [45, 46], although a pool of phosphorylated tau exists in the somatodendritic domain [47].

Tau proteins play an important role in the nucleation and stabilization of microtubules by their ability to bind to tubulin through specific domains. Transfection or microinjection of tau in cells induces its binding to microtubules, the formation of thick bundles of microtubules, and stabilizes them against depolymerizing agents.

Phosphorylation modulates the function of tau. Highly phosphorylated tau proteins are less efficient for promoting microtubule polymerization and stabilization. In the adult brain, tau exists in a range of phosphorylated states. Fetal tau show a higher phosphorylation level than adult tau [48], a situation believed to confer a more plastic and dynamic microtubule network to developing neurons.

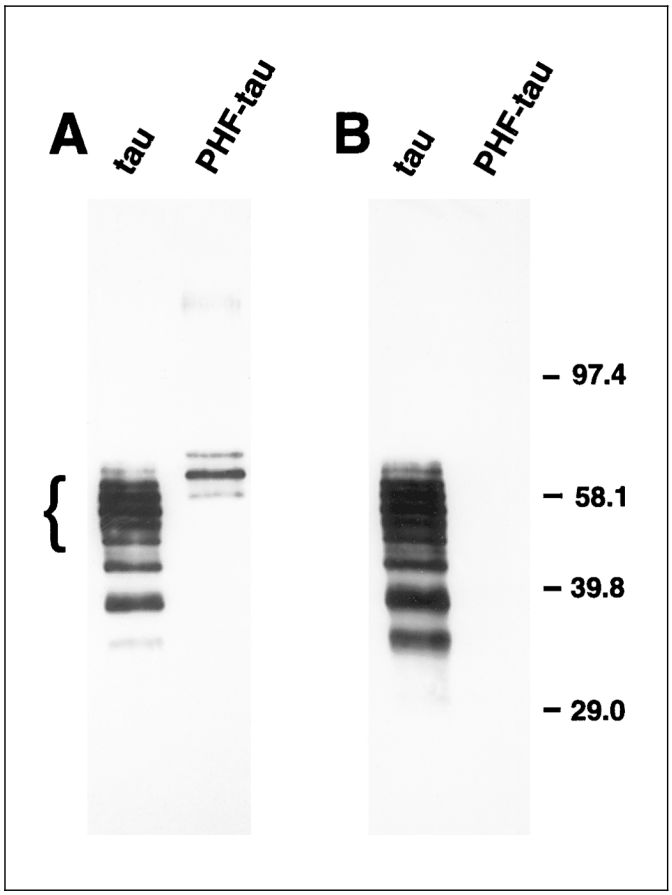

Fig. 4. Immunoblotting of purified human tau proteins and PHF-tau proteins. The blots were incubated with an anti-tau antibody insensitive to the phosphorylation status of tau (**A**) or with an anti-tau antibody recognizing a nonphosphorylated epitope on tau (tau-1 antibody) (**B**). The normal tau proteins are composed of a set of six isoforms (bracket; the bands with lower molecular weight correspond to degradation products). The PHF-tau proteins run as three major bands with slower electrophoretic mobilities, as a consequence of their high phosphorylation. The epitope of tau-1 antibody is highly phosphorylated in PHF-tau proteins, which are consequently unlabelled by the tau-1 antibody. Numbers on the right indicate the position of molecular weight markers (in kDa).

Neurofibrillary Tangles, PHF-Tau Proteins and Microtubules

PHF-Tau Proteins

PHF in Alzheimer's disease have been demonstrated to be composed of the microtubule-associated protein tau [49–55] and self-assembly of tau proteins into PHF-like filaments has been performed in vitro [56].

Tau proteins composing NFT are generally referred to as PHF-tau proteins and differ from normal tau by several posttranslational modifications, the best documented being a high state of phosphorylation [57–60]. PHF-tau is much more phosphorylated than fetal and adult autopsy-derived tau. Biopsy-derived tau is more phosphorylated than autopsy-derived tau [61] but PHF-tau can be differentiated from the former [115]. In Alzheimer's disease, PHF-tau proteins run on gels as three major bands of 55-, 64- and 69-kDa (composed of the six tau isoforms; fig. 4) [59, 62]. In progressive supranuclear palsy and in corticobasal degeneration, abnormal straight filaments are made of a 64- and 69-kDa tau doublet, and Pick bodies in Pick's disease are made of a 55- and 64-kDa tau doublet [63].

The accumulation of NFT in brain tissue is correlated with a decreased level on normal tau and increase in PHF-tau [64, 65].

It is not known if phosphorylations of tau per se is needed for PHF, although phosphorylation of tau in vitro promote the formation of tau dimers, suggested to be a key step in assembly of PHF [66]. In addition, the accumulation of phosphorylated tau in neurons, before the formation of NFT, is an early event [11, 12].

Other posttranslational modifications of PHF-tau proteins include ubiquitination [67], glycation [68], and glycosylation [69]. In situ, other molecules have been identified in NFT, e.g. MAP2 [70], APP[71], and heparan sulfate [72]. Antibodies to phosphorylated epitopes shared between neurofilaments and PHF-tau also label NFT [73]. The association of some molecules with NFT might have a physiopathological meaning: e.g. heparan sulfate induces the assembly of tau in PHF-like filaments [74] and glycation of PHF-tau could result from oxidative stress [75].

Microtubules in Alzheimer's Disease

This high state of phosphorylation of PHF-tau is believed to play a critical role, by affecting the stability of the microtubule network in neurons. This in turn would lead to disturbances of cellular functions performed by microtubules such as axoplasmic transport [76]. In ultrastructural studies, it was reported that NFT-bearing neurones are devoid of normal microtubules [77, 78] and show accumulation of membranous organelles, suggesting the existence of disturbances in axoplasmic flow [79–81].

A decrease in tubulin expression [82] and in microtubule polymerization [83] has been observed in Alzheimer's disease. PHF-tau is highly inefficient in promoting microtubule assembly [84] and can bind to normal tau, possibly sequestering the latter in a nonfunctional form [85]. The selective binding of apolipoprotein E3 to tau would protect it from becoming highly phosphorylated [86]. Tau phosphorylation was however not observed to be affected in apolipoprotein E deficient mice [87].

The Control of Tau Phosphorylation in Alzheimer's Disease

Protein Kinases

In vitro, tau proteins can be phosphorylated by the proline-directed kinases MAP kinase, the glycogen synthase kinases 3α and 3β (GSK-3α and -β), the cyclin dependent kinases cdc2, cdk2 and cdk5, the stress-activated protein kinase and by nonproline-directed kinases, including protein kinase A, protein kinase C, calmodulin-activated protein kinase, casein kinases, and the p110MARK kinase [88].

None of these individual kinases generates all the phosphorylated sites detected in PHF-tau, suggesting that several kinases might be necessary to generate fully phosphorylated PHF-tau. Available data indicate that tau proteins phosphorylated in vitro by these kinases are less efficient in promoting microtubule assembly.

Protein Phosphatases

Protein phosphatases might play an equally important role in the generation of PHF-tau proteins [89]. Phosphorylated tau proteins are an adequate substrate for phosphatase 1, 2A and 2B. The treatment of cultured neurons or tissue blocks with phosphatase inhibitors leads to the formation of highly phosphorylated tau species [90]. A tau dephosphorylation is observed after treatment with glutamate or colchicine [91], free radicals [92], increased intracellular calcium [93] and in vivo after heat shock [94] and ischemia [95]. These effects are at least in part mediated through the activation of phosphatases.

Many of the above-mentioned kinases and phosphatases have been detected in neurons containing NFT [96–99]. Relatively few data are however available on the activities of these enzymes in brain tissue in Alzheimer's disease.

Transduction Cascades

Many of the candidates kinases phosphorylating tau are key elements of metabolic cascades involved in transduction of extracellular signals. The generation of highly phosphorylated tau species in Alzheimer's disease could result from a deregulation of one or several of these cascades, leading to a disequilibrium between the activities of protein kinases and phosphatases acting on tau.

For instance, the MAP kinase is activated by growth factors, hormones and cytokines, and signalization through this cascade leads to activation of transcription factors and mitosis. However, activation of MAP kinase in intact cells did not induce the tau phosphorylation changes characteristic of PHF-tau [100].

The kinase GSK-3β is negatively regulated by the wingless/wnt pathway, a signal transduction cascade involved in developmental patterning. Expression of GSK-3β in intact cells induces a tau phosphorylation and a loss of microtubule stability [101]. In vitro phosphorylation of human brain tau by GSK-3β generates PHF-tau like proteins [102]. There is thus now good evidence that GSK-3β

is a physiological kinase for tau and participates to the generation of PHF-tau proteins.

Some phosphoepitopes found in PHF are generated by kinases involved in mitotic mechanisms [99] and their abnormal activation in neurons could engage them in a programmed cell death program. Apoptotic-like cell death in Alzheimer's disease has been reported [103], including in neurons containing NFT [104].

Neurofibrillary Tangles and the Amyloid 'Cascade'

The relationship between NFT and senile plaque remains a controversial issue in Alzheimer's research. Does one of the lesions precede and cause the other, or are they evolving independently?

A most dominant hypothesis, termed the amyloid cascade, advocates that the deposition of Aβ peptide in tissue is the primary event leading to other cellular lesions [105]. Mutations of APP and of presenilins result in increased production of Aβ and transgenic mice coexpressing mutant presenilin and APP exhibit accelerated Aβ deposition [106]. In Down's syndrome, increased production of APP leads to early Aβ deposits in cortical areas [107]. The fibrillar Aβ peptide has been reported to be neurotoxic and to induce tau phosphorylation in cell cultures [108] and in some transgenic lines the Aβ deposits are surrounded by tau-immunoreactive neurites [109].

However, several pathological and experimental data do not fit into the frame of the amyloid cascade hypothesis. NFT have been observed to appear before senile plaques in Alzheimer's disease and the two lesions develop initially in different parts of the brain [27, 29]. The in vitro neurotoxicity of Aβ peptide requires high concentration of aggregated Aβ and focal deposits of Aβ seem not toxic by themselves [110]. Transgenic animals overexpressing mutated APP or presenilin have not yet been reported to exhibit NFT and behavioural deficits have been observed in these animals before Aβ deposits [111]. A neurofibrillary pathology can also clearly develop in the absence of Aβ peptide deposits in many diseases, e.g. in amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam, corticobasal degeneration, Pick's disease, and progressive supranuclear palsy.

There is thus now strong evidence that changes of APP metabolism lead to Aβ deposits, but no clear experimental evidence that Aβ deposits induce the formation of NFT. A link between the formation of NFT and senile plaque in Alzheimer's disease could rather rely on an event affecting both the metabolism of tau and APP upstream of Aβ deposition. A direct interaction between tau and APP has also been documented [71, 112], and might play a role in the pathogenesis of NFT.

Perspectives

NFT appear as an essential neuronal lesion directly linked to neuronal dysfunction and cognitive deterioration in Alzheimer's disease. NFT formation contributes per se to this neuronal dysfunction but earlier events, i.e. the accumulation of phosphorylated tau, might play an equally important role, by disturbing the functions of microtubules. The generation of highly phosphorylated tau probably results from an imbalance between the activities of protein kinases and phosphatases involved in signalling cascades. More studies will be necessary to unravel the complexity of the control of tau phosphorylation in vivo, and how it might be affected in Alzheimer's disease.

One drawback in the study of cellular mechanisms of Alzheimer's disease is the actual lack of an animal model reproducing simultaneously all the major cellular lesions of the disease, i.e. senile plaques, neurofibrillary tangles, neuronal and synaptic loss. Some transgenic mice expressing mutant forms of APP and presenilins exhibit Aβ deposits and/or evidence of neuronal loss and behavioural deficits but not yet NFT. The overexpression of human tau proteins in transgenic mice leads to a somatodendritic accumulation of phosphorylated tau proteins, mimicking early stages of neurofibrillary degeneration but PHF formation has not yet been observed in these animals [113, 114]. Future transgenic animals expressing a combination of these and other proteins (e.g. protein kinases) will hopefully constitute powerful models for the detailed analysis of cellular mechanisms of Alzheimer's disease.

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