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Neuronal Signal Transduction and Alzheimer's Disease

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The field of Alzheimer's disease research has developed significantly over the last decade. The main proteins involved in the pathology of the disease have been identified using a combination of molecular genetics and biochemical pathology. Scientists are close to defining and integrating the neuronal signal-transduction events associated with these proteins, and to determining how this causes neuronal degeneration in Alzheimer's disease. This book brings together the expertise of some of the key researchers from diverse biochemical areas to focus upon signal-transduction dysfunction in Alzheimer's disease. Although specifically focused on Alzheimer's disease, this book has many parallels in other neurodegenerative disorders and will be of interest to those studying neuronal cell development and function in health and disease.

Front cover illustration shows the localization of presenilin 1 in a differentiated hippocampal neuron derived from a transgenic mouse cell-line expressing wild-type human protein. Photograph courtesy of Paul Fraser.

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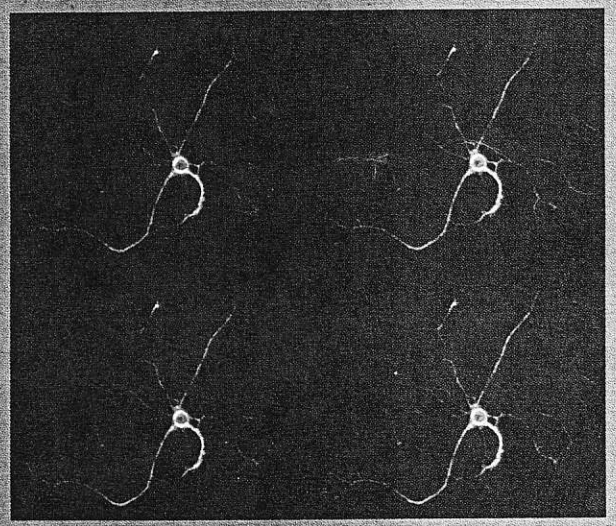

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8

Neurofibrillary tangles and tau phosphorylation

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Abstract

Neurofibrillary tangles (NFTs) are a characteristic neuropathological lesion of Alzheimer's disease (AD). They are composed of a highly-phosphorylated form of the microtubule-associated protein tau. We are investigating the relationship betweeen NFTs and microtubule stability and how tau phosphorylation and function is affected in transgenic models and by co-expression with β-amyloid precursor protein and presenilins. In most NFT-bearing neurons, we observed a strong reduction in acetylated α-tubulin immunoreactivity (a marker of stable microtubules) and a reduction of the *in situ* hybridization signal for tubulin mRNA. In transfected cells, mutated tau forms (corresponding to tau mutations identified in familial forms of frontotemporal dementias linked to chromosome 17) were less efficient in their ability to sustain microtubule growth. These observations are consistent with the hypothesis that destabilization of the microtubule network is an important mechanism of cell dysfunction in Alzheimer's disease. The glycogen synthase kinase-3β (GSK-3β) generates many phosphorylated sites on tau. We performed a neuroanatomical study of GSK-3β distribution showing that developmental evolution of GSK-3β compartmentalization in neurons paralleled that of phosphorylated tau. Studies on transfected cells and on cultured neurons showed that GSK-3β activity controls tau phosophorylation and tau functional interac-

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tion with microtubules. Tau phosphorylation was not affected in neurons overexpressing β-amyloid precursor protein. Transgenic mice expressing a human tau isoform and double transgenic animals for tau and mutated presenilin 1 have been generated; a somatodendritic accumulation of phosphorylated transgenic tau proteins, as observed in the pretangle stage in AD, has been observed but NFTs were not found, suggesting that additional factors might be necessary to induce their formation.

Introduction

The characteristic neuropathological lesions of Alzheimer's disease (AD) — senile plaques and neurofibrillary tangles (NFTs) — are present both in sporadic cases and in familial forms of the disease, indicating that they constitute a 'final common pathway' responsible for the clinical expression of the disease. Particularly, the formation of NFTs is thought to be linked closely to neuronal dysfunction and dementia in AD. In addition, mutations of the *tau* gene, whose product is the molecular component of NFTs, have recently been identified in familial forms of frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17). Some of these cases and other neurodegenerative diseases exhibit neuronal and/or glial tau-positive inclusions and have been regrouped under the term 'tauopathies' [1]. The study of the molecular composition and the mechanisms of formation of NFTs, and their effects on neuronal function, is thus believed to be essential for our understanding of the pathogenesis of AD and the other tauopathies.

NFTs are composed of bundles of abnormal filaments accumulating in neuronal perikarya, dendrites and axons. Ultrastructurally, these filaments show regular constrictions or appear straight and have been described as two filaments twisted around each other in a helical fashion, hence their name 'paired helical filaments' (PHFs). In AD, PHFs have been demonstrated to be composed of the microtubule-associated protein tau [2–4]; self-assembly of tau proteins into PHF-like filaments has been performed *in vitro* [5]. The tau proteins that PHFs are composed of are generally referred to as PHF-tau proteins and differ from normal tau by several post-translational modifications, the best documented being a high state of phosphorylation [2–4].

Since tau plays an important role in the stabilization of the microtubule network, we have investigated the relationship between NFT microtubule stability and tubulin expression in AD. Many of the phosphorylated sites identified in PHF-tau can be generated by the protein kinase glycogen synthase kinase-3β (GSK-3β). We have investigated the distribution of GSK-3β in AD and in normal rat brain, and we have studied how GSK-3β can modulate tau function in cellular models. We have also started to investigate how the phosphorylation, and some aspects of the function, of tau can be affected by overexpression in transgenic models and by co-expression with β-amyloid precursor protein (APP) and presenilins.

Microtubules in AD

Tau proteins play an important role in the nucleation and stabilization of microtubules by their ability to bind to tubulin through semi-homologous repeats localized in the half-carboxyl domain of tau. Transfection or micro-injection of tau into cells induces its binding to microtubules and the formation of thick bundles of microtubules, which it stabilizes against depolymerizing agents.

Highly phosphorylated tau proteins are less efficient at promoting microtubule polymerization and stabilization, and differential effects of phosphorylation on selected sites have been identified. The high state of phosphorylation of PHF-tau is believed to play a critical role in AD, by affecting the stability of the microtubule network in affected neurons. This in turn would lead to disturbances in the cellular functions performed by microtubules, such as axoplasmic transport [6]. In ultrastructural studies, it was reported that NFT-bearing neurons are devoid of normal microtubules [7,8] and show accumulation of membranous organelles, consistent with disturbances in axoplasmic flow [9–11]. PHF-tau is highly inefficient at promoting microtubule assembly [12] and can bind to normal tau, possibly sequestering the latter in a non-functional form [13].

To explore further the hypothesis that microtubule stability is decreased in AD, we studied the relative content of stable microtubules in neurons containing NFT, using double-immunolabelling with antibodies to tau and to acetylated α-tubulin (as a marker of stable microtubules) [14]. We observed a strong reduction in the immunoreactivity of acetylated α-tubulin in most NFT-bearing neurons, including the neuronal population with a lower tau-immunoreactivity, suggesting that reduction in acetylated α-tubulin immunoreactivity, and hence reduction in microtubule stability, could be an early event in these cells. In familial forms of FTDP-17 that are due to tau mutations, destabilization of microtubules might be favoured further by the reduced ability of mutated tau forms to sustain microtubule growth [15]. The distribution of α-tubulin mRNA in the human hippocampus of normal subjects and those with AD was also investigated by *in situ* hybridization [16]. A significant reduction in the hybridization signal was observed in areas rich in NFTs; neurons containing NFTs exhibited a weaker hybridization signal than adjacent neurons devoid of NFTs. This result suggests that tubulin transcription is reduced in NFT-bearing neurons, a reduction which might play a role in the decreased amount of microtubules in these cells.

GSK-3β: a link between tau, presenilins and APP metabolism?

Many protein kinases can phosphorylate tau *in vitro*. GSK-3β, however, is a strong candidate for a physiological kinase for tau. GSK-3β phosphorylates tau *in vitro* [17,18] and in transfected cells [19–21], and tau proteins phosphorylated by GSK-3β acquire the electrophoretic mobilities of PHF-tau proteins [22]. GSK-3β is able to modulate the activity of tau *in vitro*, rendering it less efficient in nucleating microtubule assembly [23], and thereby reducing the sta-

bility of the microtubule network in transfected cells [24]. We observed that GSK-3β is expressed in human neurons, including those containing NFT [17]. We have performed a neuroanatomical study of the distribution of GSK-3β in both the adult and the developing rat brain [25]. GSK-3β was widely expressed in neurons in most brain areas but not in glial cells. The highest expression was observed in late-embryonic and early-postnatal life. The developmental evolution of GSK-3β compartmentalization in neurons paralleled that of phosphorylated tau [26].

The mechanism by which GSK-3β can affect tau function was studied in CHO cells that had been double-transfected with tau and GSK-3β and treated with cytochalasin B. Transfection with tau induces the formation of bundles of microtubules in these cells. The weakening of the actin network by cytochalasin, as shown in other cell types [27], led to the formation of straight cell extensions containing microtubule bundles in tau-transfected CHO cells. Measurements of the length of these extensions and of the proportion of extension-bearing cells was used as a functional assay for the ability of tau to drive microtubule assembly. After double-transfection with tau and GSK-3β, the proportion of cells with extensions was strongly reduced, although their mean length was not significantly affected. This suggests that GSK-3β affects the initial nucleation step of microtubule assembly and bundling rather than the growth of microtubule bundles. This effect of GSK-3β was reversed in a dose-dependent manner by lithium, an inhibitor of GSK-3β activity [28]. We have observed that inhibition of GSK-3β activity by lithium induces a tau dephosphorylation in transfected non-neuronal cells and in cultured neurons [29].

An additional potential role for GSK-3β in the pathophysiological mechanisms of AD has been suggested by its connections with presenilins and the wingless/wnt pathway. GSK-3β is negatively regulated by the wingless/wnt pathway, a signal transduction cascade involved in developmental patterning. Inactivation of GSK-3β induces stabilization of β-catenin, which mediates wingless/wnt signalling by regulating gene expression. Presenilin 1, which is known to affect Aβ peptide formation, forms a complex with GSK-3β and β-catenin [30] that is associated with stabilization of β-catenin. Mutant presenilin 1 induces degradation of β-catenin in transgenic mice and also potentiates neuronal apoptosis. Furthermore, a reduction in β-catenin levels is observed in the brains of individuals with AD with presenilin mutations, and these mutations have been shown to cause defective trafficking of β-catenin [31]. Presenilin 1 was also observed to form a complex with GSK-3β and tau [32] and mutant presenilin 1 induced a phosphorylation of tau. If these effects are mediated by increased activity of GSK-3β, it follows that the metabolisms of tau, presenilin 1 and APP may be linked.

A molecular interaction between tau and APP has also been reported in several studies [33]. In a previous study we characterized a monoclonal antibody to tau that was generated using recombinant APP, and suggested that this might be an anti-idiotypic antibody generated against a motif involved in a binding domain between tau and APP [34]. To assess further the potential effect of APP on tau function, we studied the impact on process formation in CHO cells double-transfected with tau and wild-type APP_{695}. However, the

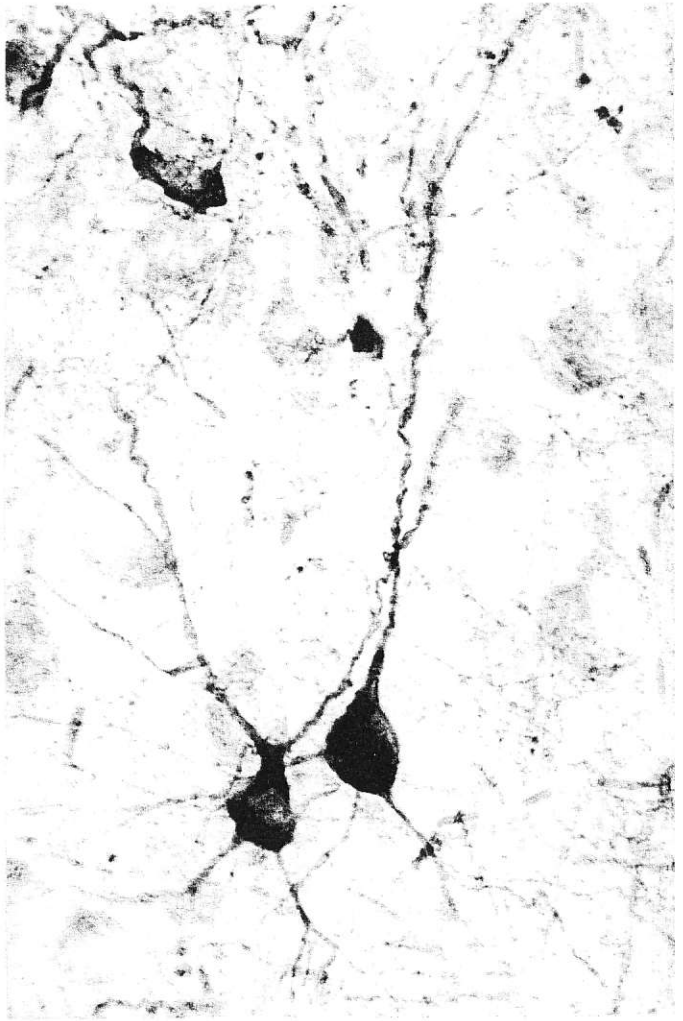

Figure 1 Immunolabelling of the entorhinal cortex of a tau transgenic mouse with the AT180 anti-tau antibody (a phosphorylation-dependent monoclonal antibody). A few neurons show a strong immunoreactivity to phosphorylated tau in their cell bodies and dendrites. Magnification × 700.

length of extensions in double-transfected cells was found not to be affected. Preliminary results using a recombinant adenovirus for the expression of human APP [35] in cultured rat neurons indicate that overexpression of APP in these neurons does not massively affect tau phosphorylation. The phosphory-

lation state of tau in these embryonic neurons is, however, already high [36], and might mask minor changes induced by expression of human APP.

Tau transgenic mice

PHF-like filaments can be generated *in vitro* using truncated [5] or full-length tau molecules in the presence of glycosaminoglycans or RNA [37,38]. In an attempt to develop a cellular model for PHF formation, we have generated transgenic mice expressing the shortest human tau isoform [39]. Transgenic tau proteins were expressed in neurons in the developing and adult brain of these mice and, using electron microscopy, the transgenic tau was detected in microtubules in axons and dendrites but not in cell bodies. NFTs were not detected in transgenic animals examined up to the age of 24 months. In contrast to the endogenous tau that progressively disappeared from neuronal cell bodies during development, the human transgenic tau remained abundant in the cell bodies and dendrites of a subset of neurons in the adult. This somatodendritic transgenic tau was immunoreactive with some antibodies to phosphorylated tau (Figure 1). It is not known whether phosphorylation of tau itself is needed for PHF formation, although phosphorylation of tau *in vitro* promotes the formation of tau dimers and is suggested to be a key step in the assembly of PHFs [40]. In addition, the accumulation of phosphorylated tau in neurons at the pretangle stage, before the formation of NFTs, is an early event [41,42]. A similar somatodendritic localization of transgenic tau proteins has been reported in another transgenic line expressing the longest tau isoform [43]. In animals transgenic for both tau and presenilin 1 [44], we observed a similar somatodendritic accumulation of the transgenic tau, but with no NFT formation up to the age of 13 months.

Conclusions

In summary, early accumulation of phosphorylated tau proteins in neuronal cell bodies observed at the pretangle stage in AD might be a consequence of changes in transduction pathways involving GSK-3β as a key step. Resulting changes in the phosphorylation state of tau would then lead to disturbances in the microtubule network. Transgenic manipulation of tau expression appears to be sufficient to affect tau compartmentalization and phosphorylation, partly as it has been observed at the pretangle stage in AD, but additional factors might be necessary to induce PHF formation.

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9

Presenilin function: connections to Alzheimer's disease and signal transduction

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Abstract

Missense mutations in presenilin 1 (PS1) and presenilin 2 (PS2) are associated with early-onset familial Alzheimer's disease which displays an accelerated deposition of amyloid plaques and neurofibrillary tangles. Presenilins are multi-spanning transmembrane proteins which localize primarily to the endoplasmic reticulum and the Golgi compartments. We have previously demonstrated that PS1 exists as a high-molecular-mass complex that is likely to contain several functional ligands. Potential binding proteins were screened by the yeast two-hybrid system using the cytoplasmically orientated PS1 loop domain which was shown to interact strongly with members of the armadillo family of proteins, including β-catenin, p0071 and a novel neuron-specific plakophilin-related armadillo protein (NPRAP). Armadillo proteins can have dual functions that encompass the stabilization of cellular junctions/synapses and the mediation of signal transduction pathways. Our observations suggest that PS1 may contribute to both aspects of armadillo-related pathways involving neurite outgrowth and nuclear translocation of β-catenin upon activation of the wingless (Wnt) pathway. Alzheimer's disease (AD)-related presenilin mutations exhibit a dominant gain of aberrant function resulting in the prevention of β-catenin translocation following Wnt signalling. These findings indicate a functional role for PS1 in signalling and suggest that

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