Published in final edited form as:
Biochem Soc Trans. 2010 August ; 38(4): 962–966. doi:10.1042/BST0380962.

Alzheimer's disease neurofibrillary degeneration: pivotal and multifactorial

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Abstract

Independent of the aetiology, AD (Alzheimer's disease) neurofibrillary degeneration of abnormally hyperphosphorylated tau, a hallmark of AD and related tauopathies, is apparently required for the clinical expression of the disease and hence is a major therapeutic target for drug development. However, AD is multifactorial and heterogeneous and probably involves several different aetiopathogenic mechanisms. On the basis of CSF (cerebrospinal fluid) levels of Aβ^{1-42} (where Aβ is amyloid β-peptide), tau and ubiquitin, five different subgroups, each with its own clinical profile, have been identified. A successful development of rational therapeutic disease-modifying drugs for AD will require understanding of the different aetiopathogenic mechanisms involved and stratification of AD patients by different disease subgroups in clinical trials. We have identified a novel aetiopathogenic mechanism of AD which is initiated by the cleavage of SET, also known as inhibitor-2 (I_2^{PP2A}) of PP2A (protein phosphatase 2A) at Asn^{175} into N-terminal (I_{2NTF}) and C-terminal (I_{2CTF}) halves and their translocation from neuronal nucleus to the cytoplasm. AAV1 (adeno-associated virus 1)-induced expression of I_{2CTF} in rat brain induces inhibition of PP2A activity, abnormal hyperphosphorylation of tau, neurodegeneration and cognitive impairment in rats. Restoration of PP2A activity by inhibition of the cleavage and of I_2^{PP2A}/SET activity offers a promising therapeutic opportunity in AD with this aetiopathogenic mechanism.

Keywords

abnormally hyperphosphorylated tau; Alzheimer's disease; microtubule-associated protein; neurofibrillary pathology; protein phosphatase 2A (PP2A); tauopathy

Introduction

AD (Alzheimer's disease), the single major cause of dementia in middle- and old-age individuals, is multifactorial and heterogeneous. Less than 1% of the AD cases are caused by a mutation in APP (β-amyloid precursor protein) or PS (presenilin) 1 or PS2 [1]. The aetiology of the remaining, i.e. over 99%, AD cases, commonly referred to as the sporadic form of the disease, is at present not established. Independent of the aetiology, AD is histopathologically characterized by the co-occurrence of β-amyloidosis and neurofibrillary

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degeneration of the brain. The former is seen as *β*-amyloid plaques and congophilic angiopathy. Neurofibrillary degeneration is seen as intraneuronal NFTs (neurofibrillary tangles) of PHFs (paired helical filaments) admixed with SFs (straight filaments) in the cell soma, in the neuropil as neuropil threads, and in dystrophic neurites surrounding the plaque core *β*-amyloid. *β*-Amyloid is made up of the APP metabolite A*β* (amyloid *β*-peptide), mostly $A\beta^{1-40}$ and $A\beta^{1-42}$ [2,3]. The major protein subunit of PHFs/SFs is the microtubule-associated protein tau in an abnormally hyperphosphorylated state [4–6]. Studies on clinicopathological correlation have repeatedly demonstrated that neurofibrillary pathology and not *β*-amyloidosis correlate with the presence of dementia in humans [7–9]. Although, according to the amyloid cascade hypothesis, *β*-amyloidosis is upstream of neurofibrillary degeneration, an increasing number of studies suggest that the latter is pivotal for at least the clinical expression of AD. Neurofibrillary degeneration of the AD type is made up of the abnormally hyperphosphorylated tau which apparently involves several different aetiopathogenic mechanisms. The present article reviews the pivotal role of the neurofibrillary pathology of the abnormally hyperphosphorylated tau and the multifactorial nature of this lesion.

Pivotal role of tau pathology in neurodegeneration and dementia

Whereas neurofibrillary degeneration and *β*-amyloidosis are two required histopathological features of AD, each of these two lesions are seen in the absence of the other in different human conditions. In a significant number of healthy aged individuals, there is as much *β*-amyloid plaque burden in the brain as in typical cases of AD, except that, in the former case, plaques lack dystrophic neurites with neurofibrillary pathology surrounding the *β*-amyloid cores [8,10–12]. On the other hand, neurofibrillary degeneration of the AD type, but in the absence of *β*-amyloid, is seen in several tauopathies such as Guam parkinsonism dementia complex, dementia pugilistica, corticobasal degeneration, Pick's disease and FTDP-17 tau (frontotemporal dementia with parkinsonism linked with chromosome 17 and tau mutations) and progressive supranuclear palsy. All of these tauopathies with neocortical lesions are clinically characterized by dementia; in progressive supranuclear palsy, the neurofibrillary degeneration is limited to the brain stem and is associated with motor impairment.

In healthy aged individuals, neurofibrillary pathology is seen in the entorhinal cortex. In AD, neurofibrillary degeneration spreads from the entorhinal cortex first to the hippocampus and then to the rest of the neocortex [13]. Apparently neurofibrillary degeneration in the neocortex is required for the dementia; neither *β*-amyloidosis of the brain in the absence of neurofibrillary degeneration nor the presence of the neurofibrillary pathology in the entorhinal cortex alone are sufficient for the clinical expression of the disease.

In the case of the inherited cases of FTDP-17, almost equal numbers are caused by a mutation in the tau gene (FTDP-17 tau) as in the TDP (TAR-DNA-binding protein)-43 gene. In FTDP-17 tau, certain missense mutations in the tau gene, including those that affect the alternative splicing of its pre-mRNA, favouring the 4R (four microtubule-binding repeat) tau isoforms, co-segregate with the disease [14–16]. These mutated taus and the 4R taus are respectively more favourable substrates for abnormal hyperphosphorylation than wild-type tau and 3R taus [17]. Inclusions of hyperphosphorylated tau have also been observed in small numbers in glial cells in the white matter, especially in frontolobal dementias [18,19].

In AD-affected brain, all of the six tau isoforms are hyperphosphorylated and aggregated into PHFs/SFs [4–6,20,21]. Although conformational changes [22–24] and truncation of tau [25–27] following its hyperphosphorylation [28] have been reported in AD, the most established and compelling cause of neurofibrillary degeneration in AD and related tauopathies is the abnormal hyperphosphorylation of this protein [5,29,30].

Two major known functions of tau are its ability to promote assembly and to maintain structure of microtubules [31]. These functions of tau are regulated by its degree of phosphorylation [29,32–34]. An increase in phosphorylation beyond the normal brain level of 2–3 mol of phosphate depresses the biological activity of tau.

As much as 40 % of the abnormally hyperphosphorylated tau in AD-affected brain is present in the cytosol and not polymerized into PHFs/NFTs [30,35,36]. Unlike normal tau, the cytosolic AD P-tau (AD abnormally hyperphosphorylated tau) does not bind to tubulin and promote microtubule assembly, but instead it inhibits assembly and disrupts microtubules [29,30,37,38]. This inhibitory property of the AD P-tau involves the sequestration of normal tau, MAP (microtubule-associated protein) 1, and MAP2 by this diseased protein [29,39,40]. This toxic behaviour of the AD P-tau appears to be solely due to its abnormal hyperphosphorylation because the dephosphorylation of the diseased tau by protein phosphatase converts it into a normal-like protein [29,37,38]. Hyperphosphorylation of tau induced by intracerebroventricular injection of forskolin, a PKA (protein kinase A) activator, in rats caused cognitive impairment and on co-administration of Rp-cAMPS (Rp isomer of adenosine 3′,5′-monophosphothioate), a PKA inhibitor, both the hyperphosphorylation and cognitive impairment were reversed [41]. The inhibitory activity of the cytosolic AD P-tau has also been confirmed in tau-transfected yeast [42,43], tau-transgenic *Drosophila* [44] and a P301L transgenic mouse model [45]. On self-assembly into PHFs/NFTs, the AD P-tau loses its ability to sequester normal MAPs and inhibit or disrupt microtubules [32,33,46].

Tau mutations, which cause FTDP-17 tau, result either in an increase in the 4R/3R tau ratio or in missense mutations. Both 4R and mutated taus are more easily abnormally hyperphosphorylated than the normal wild-type protein [17,47]. Opposite to FTDP-17 tau, in Pick's disease and Down's syndrome, the 3R/4R ratio is increased [48–50]. Since the activity of 3R tau is lesser than that of 4R tau in binding to tubulin/microtubules, the unbound 3R tau becomes abnormally hyperphosphorylated because free tau is a more favourable substrate than tau on microtubules for phosphorylation [51]. Thus it appears that a loss of the normal balance of 4R/3R taus can promote tau pathology.

Multifactorial nature of neurofibrillary degeneration

Neurofibrillary degeneration of AD P-tau, a histopathological hallmark of AD and related tauopathies, is caused by multiple factors. These multiple causes include not only mutations in the tau gene, APP gene, PS1 gene and PS2 gene mentioned above, but also metabolic abnormalities and environmental factors.

Tau is a substrate for several protein kinases [52,53]. Among these kinases, GSK3 (glycogen synthase kinase 3), Cdk5 (cyclin-dependent protein kinase 5), PKA, CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II), CK1 (casein kinase I), MAPK (mitogen-activated protein kinase) ERK1/2 (extracellular-signal-regulated kinase 1/2) and SAPKs (stress-activated protein kinases) have been most implicated in the abnormal hyperphosphorylation of tau [54,55].

The state of phosphorylation of a phosphoprotein is a function of the balance between the activities of the protein kinases and the protein phosphatases that regulate its phosphorylation. The activity of PP2A (protein phosphatase 2A), which accounts for over 70% of tau phosphatase activity in human brain [56–58] is compromised in AD–affected brain [59,60] and has been strongly implicated as a cause of abnormal hyperphosphorylation of tau [55,61,62]. On dephosphorylation with PP2A, the AD P-tau loses both its ability to inhibit microtubule assembly and self-assemble into PHFs/SFs [63]. Interestingly, this PP2A-dephosphorylated tau can be converted back into AD P-tau by more than one

combination of tau kinases, suggesting that AD neurofibrillary degeneration can involve several different aetiopathogenic mechanisms [63].

PP2A activity is regulated by two heat-stable proteins, inhibitor-1 (I_1^{PP2A}) and inhibitor-2 (I_2^{PP2A}) [64–67]. The mRNAs and protein expression of both of these PP2A inhibitors are up-regulated in AD-affected brain [68]. I_2^{PP2A}, also called SET, a primarily nuclear protein, is selectively cleaved into an N-terminal half (I_{2NTF}) and a C-terminal half (I_{2CTF}), and is translocated from the neuronal nucleus to the cytoplasm and co-localizes with NFTs in AD-affected brain [68]. Expression of I_{2CTF} in the brain causes abnormal hyperphosphorylation of tau and reference memory impairment in rats [69], suggesting a novel aetiopathogenic mechanism of neurofibrillary degeneration involving cleavage of I_2^{PP2A} and generation of I_{2CTF}.

Virtually all cases of Down's syndrome, which is caused by partial or complete trisomy 21, develop AD histopathology when they reach the fourth decade of life. In addition to APP, another important gene within the chromosome 21, Down's syndrome-critical region is *Dyrk1A*, which encodes a serine/threonine protein kinase DYRK1A (dual-specificity tyrosine-phosphorylated and -regulated kinase 1A) [70]. Recent studies suggest that overexpression of DYRK1A may cause neurofibrillary degeneration, both by leading to abnormal hyperphosphorylation of tau by priming it for further phosphorylation by GSK3*β* and by promoting exclusion of microtubule-binding repeat 2 through phosphorylation of ASF (alternative splicing factor) [50,71].

Phosphorylation of tau is also regulated by its degree of O-GlcNAcylation which involves serine/threonine residues [72,73]. O-GlcNAcylation, including that of tau, is down-regulated in AD-affected brain [74]. This is probably due to a decrease in brain glucose metabolism caused by a decrease in the level of the glucose transporters Glut1 and Glut3 [75,76]; the brain level of Glut3 is also decreased in diabetes and in cases of AD with diabetes, providing an explanation of diabetes as a risk factor and a metabolic cause of AD. All of these studies taken together suggest that the sporadic AD is multifactorial. Understanding of these different aetiopathogenic mechanisms involved is required for rational development of potent disease-modifying drugs for the treatment of AD.

Acknowledgments

We are grateful to Ms Janet Murphy for secretarial assistance. Dr Ezzat El-Akkad helped to prepare Figure 1.

Funding: Studies in our laboratories were supported in part by the New York State Office of Mental Retardation and Developmental Disabilities, National Institutes of Health [grant numbers AG019158, AG028538 and AG27429] and Alzheimer's Association (Chicago, IL) [grant numbers IIRG-00-2002, HRG-05-13095 and NIRG-08-91126].

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Abbreviations used

A*β*	amyloid *β*-peptide
AD	Alzheimer's disease
AD P-tau	AD abnormally hyperphosphorylated tau
APP	*β*-amyloid precursor protein
DYRK1A	dual-specificity tyrosine-phosphorylated and -regulated kinase 1A
FTDP-17 tau	frontotemporal dementia with parkinsonism linked with chromosome 17 and tau mutations
Glut	glucose transporter
GSK3	glycogen synthase kinase 3
MAP	microtubule-associated protein
NFT	neurofibrillary tangle
PHF	paired helical filament
PKA	protein kinase A
PP2A	protein phosphatase 2A
I_2^{PP2A}	PP2A inhibitor-2
I_{2CTF}	I_2^{PP2A} C-terminal half
PS	presenilin
R	microtubule-binding repeat
SF	straight filament

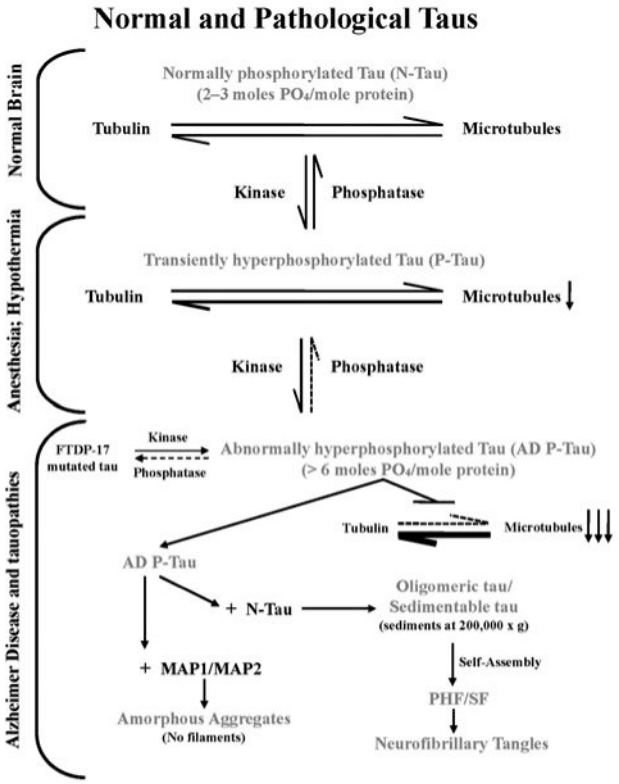

Figure 1. Multifactorial nature, pivotal role, and mechanism of AD neurofibrillary degeneration

Neurofibrillary degeneration of the AD type is a product of multiple aetiological factors. Independent of the aetiology, neurofibrillary degeneration in AD and tauopathies involves abnormal hyperphosphorylation of tau and its occurrence in the neocortex is associated with dementia; neurofibrillary degeneration in the brainstem in progressive supranuclear palsy is associated with motor impairment. A cause of hyperphosphorylation of tau is a decrease in the activity of PP2A, a major tau phosphatase. Unlike normal tau, AD P-tau, instead of interacting with tubulin and promoting its assembly into microtubules, sequesters normal tau, MAP1 and MAP2, forming 200 000 ***g*** sedimentable oligomeric tau. The sequestration of normal MAPs disrupts microtubules and compromises axonal transport and consequently retrograde degeneration and dementia. The AD P-tau polymerizes into tangles of PHFs/SFs, which, unlike the cytosolic/oligomeric AD P-tau, interacts neither with tubulin nor with normal MAPs, but eventually obstructs further the microtubule network and axoplasmic flow as a space-occupying lesion.