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Developing pharmacological therapies for Alzheimer disease

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Abstract. Alzheimer disease (AD), while chronic and progressive with an average progression of 7 – 10 years, is both multifactorial and heterogeneous. Thus, AD offers a large window of opportunity and a large number of therapeutic targets to inhibit it. The selection of a therapeutic target, however, is one of the biggest challenges in developing a pharmacological treatment of this multifactorial disease. Inhibition of a pivotal downstream event is likely to benefit more patients than inhibition of an upstream event in AD pathogenesis. Neurofibrillary degeneration of abnormally hyperphosphorylated tau offers such a pivotal therapeutic target. Abnormal hyperphosphorylation of tau and not its aggregation into filaments appears to be the most deleterious step in neurofibrillary degeneration. Tau can be abnormally hyperphosphorylated by downregulation of protein phosphatase-2A activity or by upregulation of more than one tau kinase. Restoration of the phosphatase activity which is downregulated in AD brain or inhibition of GSK-3β and cdk5, which are required for AD-type abnormal hyperphosphorylation of tau, are among the most promising therapeutic strategies.

Keywords. Alzheimer disease, tauopathies, microtubule assembly, microtubule-associated protein tau, abnormally hyperphosphorylated tau, protein phosphatase-2A, memantine, neurofibrillary pathology.

Introduction

Alzheimer disease (AD) is multifactorial and heterogeneous, and thus offers multiple pharmacological therapeutic targets. Identification of various subgroups of this disease and of its pivotal pathogenic steps can greatly facilitate the development of rational therapeutic drugs. In less than 1% of the cases the disease cosegregates with certain mutations in β-amyloid precursor proteins, presenilin-1 and presenlin-2 [1]. Over 99% of AD cases are not associated with any known mutations, and the nature of the etiological agent is not yet understood, but might involve metabolic and signal transduction abnormalities [2]. These different etiological factors may, nevertheless, lead to some common pathogenic events and vicious cycles that ultimately produce the disease clinically.

Independent of cause, AD is characterized clinically by progressive dementia and histopathologically by the presence of numerous neurofibrillary tangles and neuritic (senile) plaques with neurofibrillary changes in the dystrophic neurites [3]. While plaque amyloid is made up of largely Aβ peptide [4], the neurofibrillary tangles in the neuronal cell body and its dystrophic neurites, including those surrounding the amyloid core in the plaque, are made up of the microtubule-associated protein tau in an abnormally hyperphosphorylated state [5, 6]. In human brain, tau has six molecular isoforms, i.e., three 3-repeat and three 4-repeat isoforms. In a large number of the mature tangles tau is ubiquitinated [7 – 9]. Whereas neurofibrillary degeneration appears to be required for clinical expression of the disease, the dementia, β-amyloidosis alone in the absence of neurofibrillary degeneration does not produce the disease clinically. In fact some normal aged individuals have as much β-amyloid plaque burden in the brain as typical cases of AD, except that in the former case plaques lack

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dystrophic neurites with neurofibrillary changes surrounding the β-amyloid cores [10–14]. On the other hand, neurofibrillary degeneration of the AD type but in the absence of β-amyloidosis, which is seen in several conditions such as Guam parkinsonism-dementia complex, dementia pugilistica, frontotemporal dementia with parkinsonism linked to chromosome-17 (FTDP-17) and progressive supranuclear palsy, is associated with dementia. Furthermore, in inherited cases of FTDP-17, certain missense mutations in the tau gene co-segregate with the disease [15–17]. In this article the multifactorial nature of AD, a molecular mechanism of neurofibrillary degeneration of abnormally hyperphosphorylated tau and various pharmacological therapeutic approaches to inhibit this lesion are reviewed.

Diagnosing a specific subgroup of AD in a patient

AD can be caused by a number of different factors. Different signal transduction and metabolic factors through different disease mechanisms apparently lead to the same two common disease characteristic lesions, neurofibrillary degeneration of abnormally hyperphosphorylated tau and β-amyloidosis (Fig. 1). Therefore, identification of different AD subgroups which might represent different etiopathogenic mechanisms will not only improve the accuracy of the diagnosis but also help develop and measure the efficacy of different therapeutic drugs towards these disease subgroups.

Because of clinical heterogeneity, the diagnosis of AD remains probable till postmortem histopathological examination, and is made primarily by exclusion of other causes of dementia [18]. AD histopathology shows considerable qualitative and quantitative heterogeneity. AD can be neocortical type, limbic type and plaque-dominant type, and it may present with numerous neurofibrillary tangles exclusively confined to the hippocampus and entorhinal cortex [19]. The two most common confounding diagnoses are cerebral vascular disease (multi-infarct dementia) and dementia with Lewy bodies.

Increased rates of ventricular volume and whole brain atrophy have been demonstrated in AD [20]. The whole brain atrophy in AD brain results in a loss of brain mass of as much as ~2–3% per year compared with ~0.4–0.5% in age-matched control subjects [21]. A number of animal and human studies have suggested that $A\beta_{1-42}$ levels in cerebrospinal fluid (CSF) reflect the amyloid β pathology in the brain. Reduction of $A\beta_{1-40}$ and $A\beta_{1-42}$ in the brain of adult rats treated orally with gamma-secretase inhibitors have been found to result in decreased levels of Aβ in both brain and CSF [22, 23]. An inverse relation between in vivo amyloid load and CSF levels of $A\beta_{1-42}$ has been found in humans [24]. Antemortem CSF levels of $A\beta_{1-42}$, total tau and phosphotau-Thr_{231} have been reported to reflect the histopathological changes observed postmortem in the brains of AD cases [25, 26]. The CSF levels of tau have been shown to be markedly increased in patients with diffuse axonal injury in head trauma which revert on clinical improvement [27]. Thus, the bulk of the evidence supports that CSF reflects the state of the brain protein metabolism.

Development of therapeutic drugs requires our ability to accurately diagnose the disease and its specific subtypes, as well as the availability of specific outcome measures. We postulate that more than one disease mechanism and signaling pathway involved in producing the AD pathology, especially the neurofibrillary degeneration of abnormally hyperphosphorylated tau, and that various subgroups of AD can be identified based on the CSF levels of proteins associated with senile (neuritic) plaques and neurofibrillary tangles. In testing this hypothesis, we immunoassayed the levels of tau, ubiquitin and $A\beta_{1-42}$ in retrospectively collected lumbar CSFs of 468 patients clinically diagnosed as AD (353 CSFs) and as non-AD neurological and non-neurological cases (115 CSFs). Based on the level of these molecular markers, all subjects were subjected to the latent profile analysis to determine the assignment of each subject to a particular cluster. We found that AD subdivides into at least five subgroups based on the CSF levels of A_{1-42}, tau and ubiquitin, and that each subgroup presented a different clinical profile [28]. These five subgroups are:

AELO: AD with low $A\beta_{1-42}$, high incidence of $APOE_4$, and late onset

ATEO: AD with low $A\beta_{1-42}$, high tau and early onset

LEBALO: AD with high incidence of Lewy bodies, low $A\beta_{1-42}$, and late onset

HARO: AD with high $A\beta_{1-42}$ and recent onset

ATURO: AD with low $A\beta_{1-42}$, high tau, high ubiquitin and recent onset

Subgroups AELO, ATEO, HARO and ATURO accounted for ~50%, 22%, 5% and 1%, respectively, of the AD cases studied. Subgroup LEBALO, which contained a majority of AD cases with Lewy bodies, accounted for ~19% of the AD cases.

To classify diagnosed AD cases into the proposed subgroups, we sought a simple set of rules using the level of only one indicator protein at any stage in the classification process. Ideally, it would classify cases with a sensitivity and a specificity of no less than 90% of each category and a comparable overall level of

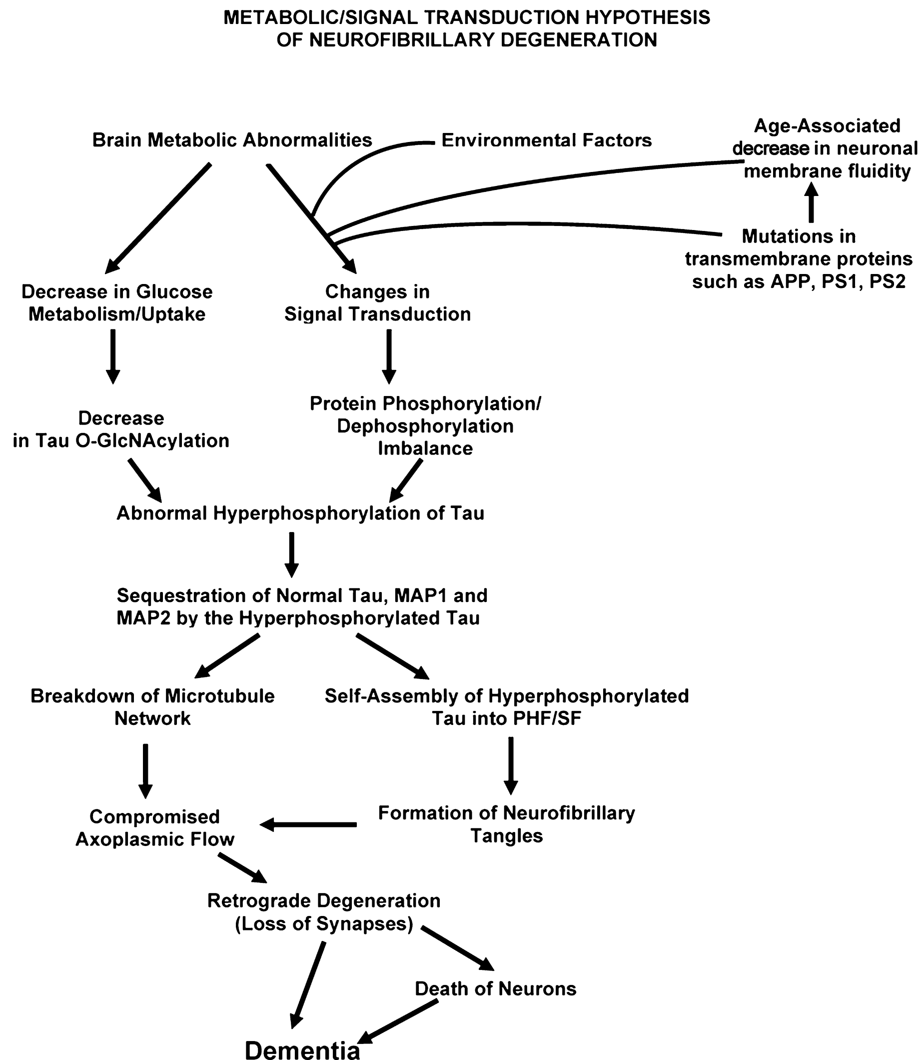

Figure 1. A schematic showing different major steps of the metabolic/signal transduction hypothesis. AD and other tauopathies require a genetic predisposition and are triggered by a variety of environmental factors, affecting one or more specific signal transduction pathways which result in a protein phosphorylation/dephosphorylation imbalance and the abnormal hyperphosphorylation of tau that leads to neurofibrillary degeneration and dementia. In AD, the protein phosphorylation/dephosphorylation imbalance in the affected neurons is generated at least in part by a decrease in the activities of tau phosphatases, i.e. PP-2A and PP-1; the activities of tau kinases such as cdk5, GSK-3, CaM kinase II and PKA might also be increased in the affected neurons. This protein phosphorylation/dephosphorylation imbalance probably involves an alteration of a specific signal transduction pathway(s) produced by an increase in the levels of an extracellular signal, e.g. FGF2 or an alteration in the molecular topology of the neuronal cell membrane or both. With age, the molecular topology of the cell membranes is altered due to a decrease in membrane fluidity. The mutations in transmembrane proteins, such as β-APP, PS1 and PS2, increase the vulnerability of the cell membrane to alteration in pathological signal transduction. The increased risk for AD in the carriers of the $APOE_4$ allele as opposed to $APOE_2$ or $APOE_3$ alleles might also involve alteration of signal transduction through the interaction of $APOE_4$ with the neuronal cell membrane. Any mutation or post-translational modification of tau that will make it a better substrate for abnormal hyperphosphorylation will also increase the risk for the disease. High cholesterol might be involved in decreasing membrane fluidity. Decreased glucose metabolism/uptake might lead to the abnormal hyperphosphorylation of tau through a decrease in its O-GlcNAcylation. [Reproduced with permission from Iqbal and Grundke-Iqbal, Acta Neuropathologica (2005) 109: 25–31].

correct classification. The algorithm must unambiguously categorize all cases. A decision tree based on the algorithm was derived based on examination of cluster characteristics and experimental runs that came closest to fulfilling those criteria (see Fig. 2). The respective sensitivities and specificities were: AELO, 90%, 92%; ATEO, 90%, 95%; LEBALO, 88%, 99%; HARO, 100% 99%; and ATURO, 100%, 100%. This study demonstrated that CSF levels of $A\beta_{1-42}$, tau and ubiquitin could diagnose AD in five different subgroups at sensitivities and specificities of greater than 88%, and overall 86% of cases were classified correctly. This rate of diagnostic accuracy not only is superior to using one of these markers individually or in combination of twos, but also exceeds the biomarker criteria of the Consensus Report [29].

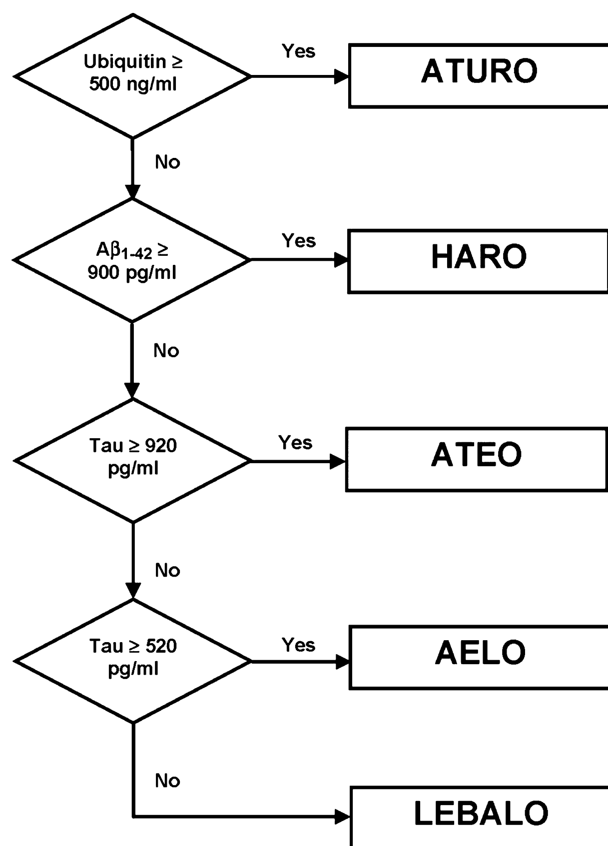

Figure 2. Decision tree for identifying various subgroups of Alzheimer disease based on CSF levels of ubiquitin, $A\beta_{1-42}$ and tau. [Reproduced with permission from Iqbal et al., Ann.l Neurol. (2005) 58:748-757].

Our recent studies have revealed that more than one signaling pathway is involved in neurofibrillary degeneration. We have found that tau can be abnormally hyperphosphorylated to self-assemble into bundles of paired helical filaments with more than one combination of protein kinases and that this phosphorylation of tau can be regulated by protein phosphatases (PP), especially PP-2A [30]. Thus, it is likely that, in future, additional subgroups of AD may be identified from phosphorylation patterns of CSF tau of AD patients.

The CSF analysis not only helps identify a specific AD subgroup of a patient but also can serve as the outcome measure of a drug treatment. We discovered that memantine inhibited abnormal hyperphosphorylation of tau in rat hippocampal slices in culture [31], and that this effect of the drug was through disinhibition of PP-2A activity [32], which we previously showed to be downregulated in AD brain [33]. Based on our finding on the restoration of PP-2A activity by memantine, Gunnarrsson et al. [34] investigated and found a significant decrease in the phosphotau level in the CSF of patients 1 year after treatment with memantine.

Because of the involvement of different etiopathogenic mechanisms in AD, the identification of different subgroups of this single major cause of age-associated dementia is critical for development of potent and specific drugs that can prevent and cure this disease. Currently, several hundred drugs for AD are under development by the pharmaceutical industry. Stratification of test subjects in clinical trials by disease subgroups may increase the chance of success up to several-fold. The future of therapeutic drugs for AD may depend on recognition of different subgroups of the disease.

Neurofibrillary degeneration: a pivotal step in the pathogenesis of AD

Neurofibrillary degeneration of the Alzheimer type is not unique to AD but is also seen in several related neurodegenerative disorders, such as frontotemporal dementias, supranuclear palsy, corticobasal degeneration, dementia pugilistica and Guam parkinsonism-dementia complex. All of these related disorders, which are collectively called tauopathies, lead to dementia. In the case of inherited cases of FTDP-17, several point mutations in tau, as well as mutations that affect the alternative splicing of its messenger RNA (mRNA) favoring the 4-repeat tau isoforms, cause this dementia [15–17]. Both these mutated taus and the 4-repeat tau become more favorable substrates for abnormal hyperphosphorylation [35]. Beta amyloidosis, the second hallmark lesion of AD, in the absence of neurofibrillary degeneration does not produce the disease clinically, suggesting the pivotal nature of the latter in the pathogenesis of AD and related tauopathies.

Mechanism of neurofibrillary degeneration

While both conformational changes [36–38] and truncation of tau [39–41] have been reported in AD, the most established and most compelling cause of dysfunctional tau in AD and related tauopathies is the abnormal hyperphosphorylation of this protein [6, 42, 43]. Tau, a phosphoprotein which normally contains 2–3 mol of phosphate/mol. of the protein [44], is abnormally hyperphosphorylated in AD brain [42] and, in this state, is the major protein subunit of the paired helical filaments/neurofibrillary tangles [5, 6, 45, 46]. Two major known functions of tau are its ability to promote assembly and to maintain the structure of microtubules [47]. These functions of tau are regulated by its degree of phosphorylation [43, 48–50].

In AD brain there is as much normal tau as in age-matched control human brain, but, in addition, the diseased brain contains 4–8-fold of abnormally hyperphosphorylated tau [51, 52]. As much as 40% of abnormally hyperphosphorylated tau is present in the cytosol and not polymerized into paired helical filaments/neurofibrillary tangles [44].

The tau polymerized into neurofibrillary tangles is apparently inert and neither binds to tubulin nor promotes its assembly into microtubules [49, 50, 53]. In contrast, the AD cytosolic abnormally hyperphosphorylated tau (AD P-tau) not only is unable to bind to tubulin and promote microtubule assembly, but also inhibits assembly and disrupts microtubules [43]. This toxic property of the pathological tau involves the sequestration of normal tau by the diseased protein [43, 54]. The AD P-tau also sequesters the other two major neuronal microtubule-associated proteins MAP1 A/B and MAP2 [55]. This toxic behavior of the AD P-tau appears to be solely due to its abnormal hyperphosphorylation, because dephosphorylation of diseased tau converts it into a normal-like protein [43, 56, 57]. Furthermore, in vitro dephosphorylation of neurofibrillary tangles disaggregates filaments, and as a result the tau released behaves like normal protein in promoting microtubule assembly [56]. Tau mutations, which cause FTDP-17, result either in an increase in the 4-repeat:3-repeat tau ratio or in missense mutations in the protein. Both 4-repeat tau and the mutated protein are more abnormally hyperphosphorylated than the normal wild-type protein [35, 58]. Thus, inhibition of abnormal hyperphosphorylation of tau should inhibit neurofibrillary degeneration and consequently the diseases characterized by this lesion.

Involvement of different signal transduction pathways in abnormal hyperphosphorylation of tau and neurofibrillary degeneration

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. Tau, which is phosphorylated at over 38 serine/threonine residues in AD [59, 60], is a substrate for several protein kinases [61, 62]. Among these kinases, glycogen synthase kinase-3 (GSK-3), cyclin-dependent protein kinase-5 (cdk5), casein kinase-1 (CK-1), protein kinase A (PKA), calcium and calmodulin-dependent protein kinase-II (CaMKII), mitogen activated protein (MAP) kinase ERK 1/2, and stress-activated protein kinases have been most implicated in abnormal hyperphosphorylation of tau [63, 64]. A large number of the abnormally hyperphosphorylated sites in tau are proline-directed, i.e. serine/threonine followed by proline, which are canonical sites of proline-directed protein kinases (PDPKs). All the three major PDPKs, GSK-3β, cdk5 and ERK 1/2, have been shown to phosphorylate tau at a large number of the same sites seen in AD.

GSK-3β and cdk5 phosphorylate tau at a large number of sites, most of which are common to the two enzymes [65, 66]. The expressions of GSK-3β and cdk5 are high in the brain [67–69], and both enzymes have been shown to be associated with all stages of neurofibrillary pathology in AD [70, 71]. Overexpression of GSK-3β in cultured cells and in transgenic mice results in hyperphosphorylation of tau at several of the same sites seen in AD, and inhibition of this enzyme by lithium chloride attenuates phosphorylation in these models [72–79].

Cdk5 requires for its activity interaction with p39 or p35 or, better, their proteolytic products p29 or p25, respectively, which are generated in post-mitotic neurons by digestion with calpains [80, 81]. Overexpression of p25 in transgenic mice, which results in an increase in the activity of this enzyme, also produces hyperphosphorylation of tau [82, 83].

The MAP kinase family, which includes ERK1, ERK2, p70S6 kinase and the stress-activated kinases JNK and p38 kinase, have been shown to phosphorylate tau at several of the same sites as the abnormally hyperphosphorylated tau and so has the association of these enzymes with the progression of neurofibrillary degeneration in AD [64, 84–89].

Unlike the PDPKs, the non-PDPKs have been shown to phosphorylate tau at only a few of the sites. CaMK II phosphorylates tau at Ser-262/356 and at Ser-416 [90–93]. Both PKA and MARK kinase have also been shown to phosphorylate tau at Ser-262 [94–96]. However, phosphorylation of tau by these non-PDPKs markedly increases the phosphorylation of tau by PDPKs, GSK-3β and cdk5 [65, 97–99]. The priming of tau by PKA appears to be sufficient to promote the abnormal hyperphosphorylation of tau by the basal level of GSK-3β activity in normal adult rat brain and to lead to impairment of spatial memory in these animals [100]. Although, to date, the activities of these protein kinases, except GSK-3β, have not been reproducibly shown to be upregulated in AD brain, transient stimulation of these enzymes, especially the priming kinases such as PKA or CaMKII, might be sufficient to result in the abnormal hyperphosphorylation of tau.

The activities of protein phosphatase (PP)-2A and PP-1 are compromised by ~20–30% in AD brain [33, 101], and the phosphorylation of tau that suppresses its microtubule binding and assembly activities in adult mammalian brain is regulated by PP-2A and not

by PP-2B [93, 102]. PP-2A accounts for over 70% of all phosphoseryl/phosphothreonyl activity in human brain [103]. PP-2A also regulates the activities of several tau kinases in brain. Inhibition of PP-2A activity by okadaic acid in cultured cells and in metabolically active rat brain slices results in abnormal hyperphosphorylation of tau at several of the same sites as in AD, not only directly by a decrease in dephosphorylation but also indirectly by promoting the activities of CaMK II [93], PKA [31, 104], MAPK kinase (MEK1/2), extracellular regulated kinase (ERK 1/2) and P70S6 kinase [64, 88]. Thus, barring the fact that tau is not the only neuronal substrate of these protein kinases and phosphatases, it should be possible to inhibit the abnormal hyperphosphorylation of tau by inhibiting the activity of one or more tau kinases and or restoring or upregulating the activity of PP-2A.

Although the brain has several tau phosphatase activities [105, 106], PP-2A and PP-1 make more than 90% of the serine/threonine protein phosphatase activity in mammalian cells [107]. The intracellular activities of these enzymes are regulated by endogenous inhibitors. PP-1 activity is regulated mainly by a 18.7-kDa heat-stable protein called inhibitor-1 (I-1) [108, 109]. In addition, a structurally related protein, DARPP-32 (dopamine and cAMP-regulated phosphoprotein of apparent molecular weight 32 000) is expressed predominantly in the brain [110]. I-1 and DARPP-32 are activated on phosphorylation by PKA and inactivated at basal calcium level by PP-2A. Thus, inhibition of PP-2A activity would keep I-1 and DARPP-32 in active form and thereby result in a decrease in PP-1 activity. In AD brain a reduction in PP-2A activity might have decreased PP-1 activity by allowing the upregulation of I-1/DARPP-32 activity.

PP-2A is inhibited in mammalian tissue by two heat-stable proteins: (i) I_1^{PP2A}, a 30-kDa cytosolic protein [111] that inhibits PP-2A with a Ki of 30 nM and (ii) I_2^{PP2A}, a 39-kDa nuclear protein that inhibits PP-2A with a Ki of 23 nM [111]. Both I_1^{PP2A} and I_2^{PP2A} have been cloned from human kidney [112, 113] and brain [114]. I_1^{PP2A} has been found to be the same protein as the putative histocompatibility leukocyte antigen class II-associated protein (PHAP-1). This protein, which has also been described as mapmodulin, pp32 and LANP [115], is 249 amino acids long and has apparent molecular weight of 30 kDa on SDS-polyacrylamide gel electrophoresia (PAGE). I_2^{PP2A}, which is the same as TAF (template-activating factor)-1β or PHAPII, is a nuclear protein that is a homologue of the human SETα protein [116]. In AD brain there is a shift from nuclear to cytoplasmic localization of I_2^{PP2A} [117]. Both I_1^{PP2A} and I_2^{PP2A} interact with the catalytic subunit of PP-2A [118]. The level of I_1^{PP2A} is ~ 20% increased in AD brains as compared with age-matched control brains, which probably is a cause of the decrease in PP-2A activity in AD brain.

Hyperphosphorylation promotes the assembly of tau into PHF/SF [119]. In vitro studies have demonstrated that phosphorylation of tau to ~4–6 mol/mol of the protein converts it into an AD P-tau-like state, i.e. where instead of promoting it inhibits microtubule assembly by sequestering normal tau and other MAPs. On further hyperphosphorylation to ~9–12 mol phosphate/mol of the protein, tau self-assembles into PHF/SF. The FTDP-17 mutated taus are more readily hyperphosphorylated than the normal/wild-type human brain tau, become inhibitory and self-assemble into PHF/SF at a lower stoichiometry of phosphorylation than the corresponding wild-type protein [35]. Abnormally hyperphosphorylated tau from AD brain cytosol, the AD P-tau, self-assembles into bundles of PHF/SF [119, 120]. On treatment with PP-2A, which dephosphorylates most of the known abnormally hyperphosphorylated sites, including Thr-231 and Ser-262, the AD P-tau loses its ability both to inhibit microtubule assembly and to self-assemble into PHF/SF [120]. Rephosphorylation of the PP-2A dephosphorylated AD P-tau, the PP2A-AD P-tau, by PKA followed by CaMKII and GSK-3β, or cdk5, or cdk5 followed by GSK-3β, results in phosphorylation of Thr-231 and Ser-262 among several other sites, and restores its ability to inhibit microtubule assembly and self-assemble into PHF/SF. The bundles of filaments formed under these conditions are congophilic and very reminiscent of the neurofibrillary tangles seen in AD brain. Rephosphorylation of PP-2A-AD P-tau by none of the above kinases individually, however, phosphorylates at both Thr-231 and Ser-262 and restores its self-assembly into PHF/SF. Thus, these studies [120] revealed that more than one specific combination of kinases is involved in converting normal tau into an AD P-tau-like state, and that PP-2A can alone convert the pathological state of the protein to a normal-like state. These findings suggest that activation of PP-2A and/or inhibition of both GSK-3β and cdk5 are among the most promising therapeutic targets for inhibition of neurofibrillary degeneration in AD and related tauopathies.

Memantine, an anti-AD drug and an NMDA receptor antagonist, inhibits the abnormal hyperphosphorylation of tau by restoring the PP-2A activity in rat hippocampal slices in culture in which the PP-2A activity was inhibited by okadaic acid [31]. The restoration of the PP-2A activity appears to be due to the binding of memantine to I_2^{PP2A} and disinhibition of its activity towards P-tau [32]. The CSF level of phosphotau is significantly reduced in AD patients after one year treatment with memantine [34]. These

findings suggest that PP-2A is a promising therapeutic target for AD and related tauopathies.

Involvement of decreased brain glucose metabolism in neurofibrillary degeneration

In addition to abnormal hyperphosphorylation, tau is also abnormally glycosylated, and the latter appears to precede the former in AD brain [121, 122]. In vitro studies indicate that abnormal glycosylation promotes tau phosphorylation with PKA, GSK-3β and cdk5, and inhibits dephosphorylation of tau with PP-2A and PP5 [123, 124]. In addition, like some other neuronal phosphoproteins, tau is also O-GlcNAcylated [125, 126]. In contrast to classical N- or O-glycosylation, O-GlcNAcylation, which involves the addition of a single sugar at serine/threonine residues of a protein, dynamically post-translationally modifies cytoplasmic and nuclear proteins in a manner analogous to protein phosphorylation (see [127]). O-GlcNAcylation and phosphorylation reciprocally regulate each other. In AD, probably due to impaired glucose uptake/metabolism, the O-GlcNAcylation of tau is significantly reduced, and decreased glucose metabolism in cultured cells and in mice, which decreases the O-GlcNAcylation of tau, produces abnormal hyperphosphorylation of this protein [128].

Therapeutic approaches to inhibit neurofibrillary degeneration

Neurofibrillary degeneration of abnormally hyperphosphorylated tau is downstream but pivotally involved in the pathogenesis of AD and related tauopathies, and thus inhibition of this lesion is likely to arrest these diseases, which are products of multiple etiopathogenic mechanisms. The most promising therapeutic approaches to inhibit neurofibrillary degeneration and consequently AD are (1) to inhibit the abnormal hyperphosphorylation of tau and (2) to inhibit sequestration of normal MAPs by the AD P-tau. The former can be carried out apparently best by inhibiting activities of both GSK-3 and cdk5, by activating PP-2A activity or by increasing brain glucose uptake/metabolism, which could enhance O-GlcNAcylation and consequently an inhibition of the abnormal hyperphosphorylation of tau. Memantine, a low-to- moderate affinity NMDA receptor antagonist which improves mental function and the quality of daily living of patients with moderate-to-severe AD [129, 130], restores PP-2A activity, the abnormal hyperphosphorylation of tau at Ser-262 and the associated neurodegeneration in hippocampal slice cultures from adult rats, and PC-12 cells in culture [31, 32]. Furthermore, restoration of PP-2A activity to normal levels by memantine also results in restoration of the expression of MAP2 in the neuropil and reversal of hyperphosphorylation and the accumulation of neurofilament H and M subunits. Memantine, however, is a positively charged molecule and probably enters a neuron only during excitotoxicity when the NMDA receptor channels are open. Therefore, its therapeutic benefit might be limited to only those patients and/or the advanced states of the disease when there is persistent excitotoxicity. Generation of cell-permeable memantine-like compounds can help develop potent therapeutic drugs for AD and related tauopathies.

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