ELSEVIER

Archives of Medical Research 41 (2010) 226–231

Archives of Medical Research

OPINION

The Revitalized Tau Hypothesis on Alzheimer's Disease

Ricardo B. Maccioni, Gonzalo Farías, Inelia Morales, and Leonardo Navarrete

Laboratory of Cellular and Molecular Neurosciences, Faculty of Sciences, University of Chile & International Center for Biomedicine (ICC), Edificio Milenio, Las Encinas, Ñuñoa, Santiago, Chile

Received for publication February 19, 2010; accepted March 1, 2010 (ARCMED-D-10-00083).

Many hypotheses have been raised regarding the pathophysiology of Alzheimer's disease (AD). Because amyloid beta peptide (Aβ) deposition in senile plaques appears as a late, nonspecific event, recent evidence points to tau phosphorylation and aggregation as the final common pathway in this multifactorial disease. Current approaches that provide evidence in favor of neuroimmunomodulation in AD and the roles of tau pathological modifications and aggregation into oligomers and filamentous forms are presented. We propose an integrative model on the pathogenesis of AD that includes several damage signals such as Aβ oligomers, oxygen free radicals, iron overload, homocysteine, cholesterol and LDL species. These activate microglia cells, releasing proinflammatory cytokines and producing neuronal degeneration and tau pathological modifications. Altered and aggregated forms of tau appear to act as a toxic stimuli contributing to neurodegeneration. Recent findings provide further support to the central role of tau in the pathogenesis of AD, so this protein has turned into a diagnostic and therapeutic target for this disease. © 2010 IMSS. Published by Elsevier Inc.

Key Words: Alzheimer's disease, Neuronal cells, Activation of microglia, Proinflammatory factors, Damage signals, Tau phosphorylations, Tau oligomers.

Introduction

Alzheimer's disease (AD) is one of the human disorders that has triggered the largest number of hypotheses to explain its pathogenesis, possibly strengthened by the fact that no cure has yet been found for this devastating disease. Unfortunately, none of these hypotheses accounted coherently for the diversity of the initial events that trigger neurodegeneration and that result in the deposition of senile plaques (SP) and neurofibrillary tangles (NFTs). The most commonly held amyloid hypothesis, prevailing for over two decades, has broken as a result of solid evidence that SP do not account for the complex pathophysiology of AD, and the fact that these structures are not pathognomonic for the disease. Recent findings pointing to unpleated Aβ oligomers as responsible for synaptic impairment, indicate that these oligomers are only one among several other damage signals affecting the integrity of brain function. Amyloid deposits thus appear to be a rather late event and have even been postulated to have a neuroprotective role.

In this context, the early tau hypothesis strengthens in light of observations that tau oligomers are neurotoxic, clinical correlations with tau pathology and the fact that anomalous tau hyperphosphorylations constitute a common final pathway for the different altered molecular signals that affect brain neurons. This raises the question as to precisely what triggers the pathological phosphorylations. We postulated that a series of damage signals that include, among other factors, Aβ oligomers, oxygen free radicals, iron overload, cholesterol levels in neuronal rafts, LDL species and homocysteine trigger, by innate immunity, the activation of microglial cells with the consequent release of proinflammatory cytokines that modify neuronal behavior through anomalous signaling cascades that finally promote tau hyperphosphorylation. Tau modifications lead to its oligomerization and the long-term production of NFTs. As a result of neuronal death, oligomeric forms and tau filaments are released to the extracellular environment, contributing to activation of microglial cells and stimulating the deleterious cycle leading to progressive neuronal degeneration.

Address reprint requests to: Dr. R.B. Maccioni, Laboratory of Cellular and Molecular Neurosciences, Universidad de Chile, Edificio Milenio, Las Encinas 3370, Ñuñoa, Santiago, Chile; Phone: 562-978-7228; E-mail: rmaccion@manquehue.net or http://www.ricardomaccioni.com

0188-4409/$–see front matter.
doi: 10.1016/j.arcmed.2010.03.007

The Tau Protein in AD

More than a century ago, the discovery by Alois Alzheimer of NFTs in the brains of patients with the neurodegenerative disorder named after him (Alzeimer's disease) provided the basis for a significant amount of studies to elucidate the molecular, cellular and genetic features of this disease (1−3). However, the discovery that the protein components of NFTs and the paired helical filaments (PHFs) were hyperphosphorylated forms of tau was achieved only during the 1980s (4). Many studies have improved our understanding of tau hyperphosphorylation, changes in tau interaction patterns with microtubules, and alteration of the neuronal cytoskeleton (5,6), whereas recent reports have shed light on the mechanisms of tau self-polymerization.

AD is a multifactorial disorder in which protein alterations, oxidative stress, neuroinflammation, immune deregulation, impairment of neuronal−glial communication, and neurotoxic agents appear among factors triggering neuronal degeneration, and the balance among these may vary from patient to patient. Although diverse, these factors induce deleterious signaling through different sets of neuronal receptors that finally converge in the hyperphosphorylation of tau molecules.

Structural studies, together with the elucidation of the signaling cascades in neurodegeneration, led us to postulate a hypothesis based on the concept that tau hyperphosphorylation constitutes a final common pathway in AD pathogenesis, upon which a host of signaling mechanisms converge, and that this phenomenon precedes widespread neuronal degeneration (7−9). In this context, the tau hypothesis is based on converging neurobiological studies (10−12) and clinical data sets (13,14). Actually, increasing evidence indicates that the tau hypothesis provides the closest approximation to clinical observations on AD patients. Among these, (i) severity on this type of dementia correlates well with the increasing accumulation of NFTs in the brain (3,13), (ii) the high correlation between the hyperphosphorylated tau species in the cerebrospinal fluid (CSF) of AD patients with the extent of cognitive impairment (14) and (iii) that a decrease in tau filaments by target-directed drugs alleviate cognitive impairment (15).

The establishment of an experimentally testable unifying hypothesis on AD is the basis on which to build innovative diagnostic and therapeutic approaches. The unchallenged acceptance of the amyloid hypothesis for about two decades (16,17) has led to unsuccessful efforts to generate drugs to control AD because pleated amyloid and SPs are most probably not the cause of neuronal degeneration (16), and the expectations harbored on antiamyloid therapies will most likely not materialize. The revised version of the most commonly held amyloid hypothesis (17) rests on the concept that Aβ (1−42) self-polymerizes over years to form SPs, which then trigger subsequent brain lesions. However, SPs are also common in neurologically healthy individuals and not unique to AD. Unpleated Aβ oligomers (ADDLs) rather than SPs appear to be the elements responsible for synaptic impairment well before the accumulation of fibrillary amyloid (18). On the basis of these findings and evidence of tau filament formation, followers of the tau hypothesis have pointed to the fact that tau aggregation and neurotoxicity associated with the hyperphosphorylated forms constitute common events determinant for the neurodegenerative cascade.

We focus our discussion on the updated tau hypothesis together with our current neuroimmunomodulation concepts that provide a novel unifying hypothesis of AD pathophysiology that account coherently for almost all known facts on AD and point the way for subsequent efforts toward its elucidation. Therefore, information obtained in the process of testing this new hypothesis experimentally will likely be helpful to formulate an innovative AD therapy and to design reliable biomarker strategies for its diagnosis (19). Thus, beyond the classical formulation of the tau hypotheses, the recent postulates on the role of neuroimmunomodulation changes in the pathogenesis strengthen the idea that damage signals activate microglia, which in turn overproduce proinflammatory cytokines that trigger deleterious signal cascades in neuronal cells (8) with deregulation of protein kinases and phosphatases controlling tau phosphorylations and the consequent neurofibrillary degeneration. As a result of neuronal death, tau oligomeric species are released into the extracellular environment, thus contributing to microglial activation and providing positive feedback on the deleterious cycle that lead to progressive degeneration of neurons in AD brains (20).

Anomalous Signaling and Tau Hyperphosphorylation and Oligomerization

The low molecular weight microtubule-associated protein (MAP) tau is the major component of the MAPs in axons and plays critical roles in stabilizing microtubules and inducing its own assembly (6). However, under pathological conditions tau self-aggregates into PHFs, which turn into the NFTs during the course of AD, a neuropathological hallmark of AD and tauopathies (21,22). Recent studies indicate that hyperphosphorylated tau oligomers exert pathological effects, triggering neurotoxic actions that affect the normal interaction patterns of the neuronal cytoskeleton (23). Pathological tau oligomerization seems to correlate with cognitive impairment (24). Important advances toward our understanding on *in vitro* tau polymerization have contributed to clarify the molecular mechanisms (25−27) even though the structural transitions from the native conformation of tau to its neurotoxic polymers remains to be elucidated.

It has been shown that polyanions that promote PHF aggregation as well as microtubules interact with tau through positive charges near the ends of tau repeats (28) and through the β-structure forming-motifs at the beginning

of repeats 2 and 3. The binding nature of polyanions supports the hypothesis that stable microtubules prevent PHF formation by blocking tau–polyanion interaction sites, which are crucial for anomalous PHF formation (29). Moreover, tau oligomers with a prefilamentous structure appear to play a role at early stages of AD and tauopathies but also in asymptomatic patients with Braak-stage I neuropathology where clinical symptoms of AD and NFTs in frontal cortex are absent. This suggests that an increase in tau oligomers occurs before individuals manifest clinical symptoms of AD. Interestingly, ligands of the family of quinolines and derivatives with high affinity for tau oligomers control tau polymerization (30), thus offering an avenue toward generation of potential tau-aggregation inhibitory drugs for treatment of AD.

Research on the pathophysiology of the major molecular factors triggering AD has provided clues on the structural–functional underpinnings of tau–tau interactions (31) as well as on the links between Aβ production and tau hyperphosphorylations (32,33). According to our unifying hypothesis—built on the role of tau as a final common effector pathway—abnormal signaling leading to degenerative processes starts with the continuous activity of individually variable factors such as oxidative agents (34), iron overload (35), disorders of lipid metabolism, hyperglycemia, deregulation of insulin levels (36), chronic infections, head trauma, and others (8). These factors are likely to activate endogenous alarm signals that trigger anomalous cellular signaling cascades in microglial cells and astrocytes (Figure 1).

In turn, activated glial cells respond by releasing NF-κB and overproduce proinflammatory cytokines (TNFα, Il-6, IL-1β), thus leading to brain inflammation (37) and serious alterations in neuron–glia interaction patterns (20,38). Interestingly, overproduction of IL-6 activates the JAK/Stat system via IL-6 and/or NMDA receptors, which in turn activates MAP kinases, thus promoting the activity of transcription factor Egr-1 that increases p35 expression. This latter effect results in the activation of cdk5 protein kinase involved in neuronal development (32) with subsequent tau hyperphosphorylation. Activation of the kinase p38 also results in tau hyperphosphorylations (39). Moreover, IL-6 and TNFα also activate specific neuronal receptors, inducing cell cycle activity without proliferation. One of the critical kinases involved in neuronal development, cdk5, is deregulated in AD according to *in vitro* evidence, studies in animal models with tau pathology (33), and studies in the human brain. Hence, deregulation of cdk5 results in tau hyperphosphorylation at Ser 202 and Thr 205. Inhibitors of cdk5 control tau hyperphosphorylation, neuronal degeneration, and neuronal death. Thus, deregulation of the sensitive equilibrium between protein kinases and phosphatases is critical in the degenerative phenotype of neurons (34).

Anomalous cascades mediated by tau hyperphosphorylations have alo been reported in several pathological pathways in neurons such as p75 activated by an excess of NGF (or altered processing of NGFs) produced by Aβ-activated astrocytes (40), NO effects (41), direct action of Aβ oligomers on neuronal synapses, toxicity of advanced glycation end-products (AGEs) via AGEs receptors (RAGEs) (42), downstream the degenerative cascade where hyperphosphorylated tau appears to be a final common pathway for neuronal degeneration associated with AD. Hyperphosphorylated tau species and other modified tau variants have the tendency to self-aggregate. Thus, a long-term process of anomalous tau modifications and aggregation will affect neuron function and eventually will result in neuronal death with the consequent release of tau oligomeric species and filaments. This, in turn, triggers microglia activation. In this context, through a positive feedback mechanism, anomalous tau-induced activation of microglia cells will re-activate the cycle leading to activation of the inflammatory cascade (20,30) with the subsquent death of neuronal populations (Figure 1). This evidence provides further support to the tau hypothesis and the scientific background to build future therapeutic avenues based on the inhibition or the disassembly of tau filaments.

Tau Filaments as Therapeutic Targets for AD

The characteristic qualitatively abnormal hyperphosphorylation of tau is the common denominator of all tauopathies and AD (43). In transgenic mice, the onset of pathology and functional impairment is not evidenced prior to the emergence of this biochemical hallmark. This suggests that with or without mutations on tau, it is the hyperphosphorylation and subsequent tau aggregation that converts a latent problem into active pathology during aging. Inhibition of this process is therefore highly plausible to prevent, retard, or possibly reverse—even partially—AD. Even though transgenic models of tauopathy based on tau mutations have been available since the year 2000, only few reports of their use for therapeutic purposes have been published. Focusing on abnormal conformations of mutant tau, hsp90 inhibitors have been tested in the JNPL3 mouse model with spinal cord pathology and motor phenotype (44). Inhibition of heat-shock protein (hsp90) leads to reduced chaperone activity and enhanced degradation of the mutant tau over normal tau protein. This leads to reduced formation of sarcosyl-insoluble PHF-tau species, frequently used as a biochemical model to pathologically define NFTs. However, the relationship of these operationally defined species to the overall scope of tau hyperphosphorylation is less certain than generally assumed. It is unclear whether this approach would be viable in the much more frequent tauopathies not driven by tau mutations, where tau levels may be unresponsive to hsp90 inhibition. In view of this concern, mutant tau transgenic models may not be particularly representative for AD in this specific approach. On the other hand, the levels of a host of other proteins not involved in pathology are likely to be affected in view of the normal function of hsp90.

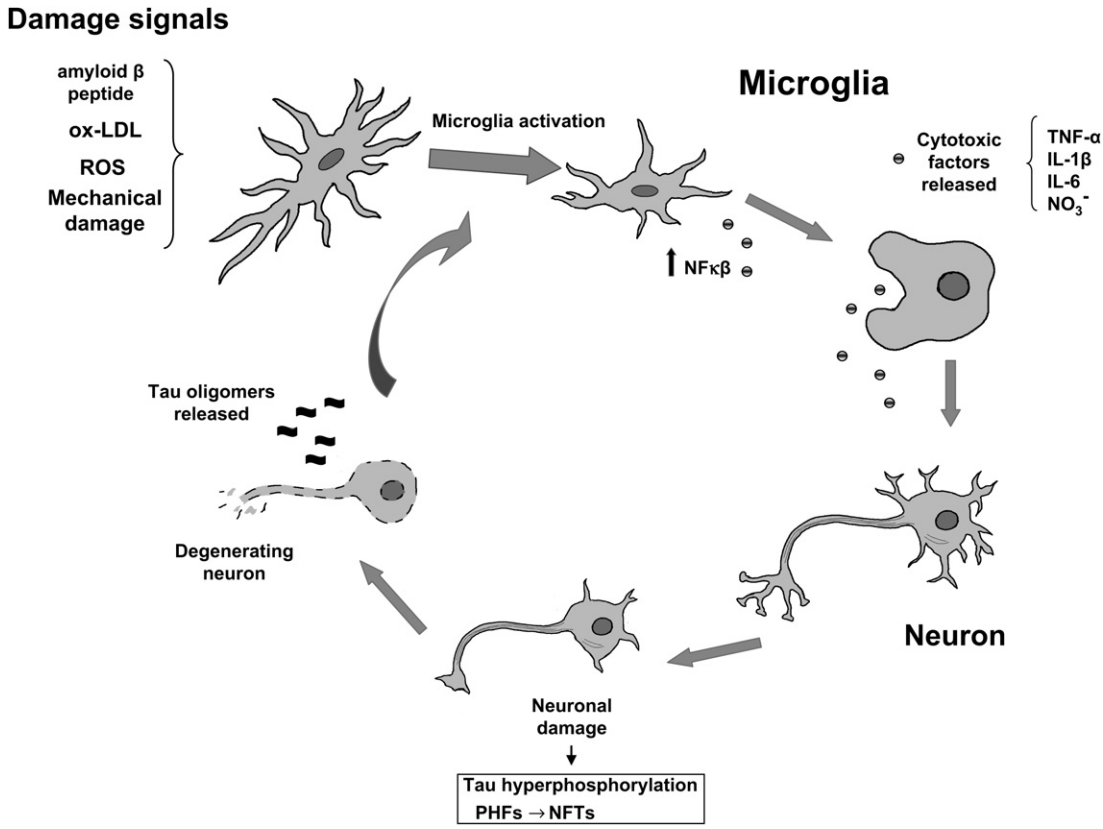

Figure 1. Model of microglial activation leading to neurodegeneration. Microglia cells sensitive to different damage signals are overactivated in the long term, resulting in an activated, amoeboid phenotype and the secretion of cytotoxic compounds (mainly pro-inflammatory cytokines) leading to neuronal damage and tau hyperphosphorylation and aggregation to form tau oligomers, PHFs and NFTs. When the neuron degenerates tau aggregates are released to the extracellular environment and act as a new damage signal contributing to the deleterious cycle of microglial cells activation.

Other studies using mutant tau transgenic mice directly address inhibition of tau hyperphosphorylation. Because GSK3β has been implicated as a tau kinase, JNPL3 mice were treated with therapeutic levels of lithium, a specific GSK3 inhibitor (45). There was a reduction in pathological markers when applied before the age of symptom onset, but it is questionable whether this was related to GSK3 inhibition in view of the increasing recognition of lithium as an enhancer of autophagy. In any case, a retardation of functional impairment was not seen with this treatment, which corroborates results discussed below that the generally used pathological markers of tauopathy, which biochemically represent downstream products, may not be the dominant toxic tau species. Significant efficacy, even at ages around disease onset, on the level of abnormally hyperphosphorylated tau species as well as for onset and/or progression of motor impairment in the same model was observed with the orally bioavailable and brain-penetrating compound SRN-003-556, exhibiting a broader kinase inhibitory spectrum (46). This compound was developed on the basis of efficacy in cell models of tau hyperphosphorylation induced by the mainly PP2A inhibiting agent okadaic acid, which are the only models where all criteria of PHF-type tau hyperphosphorylation become manifest. Only inhibitors that include those for ERK2 were active in this model, although inhibition of ERK2 alone was not sufficient. Consequently, SRN-003-556 was optimized with ERK2 as a lead assay, although collateral inhibitory activities are probably relevant as well. An observation in this study was the apparent uncoupling of tau hyperphosphorylation, determined by biochemical means from pathologically assessed NFT counts.

Therapies against Tau Aggregation

Considering the theoretical background supporting a neurotoxic role of tau modifications and aggregation in AD, attention has been focused during recent years to tau aggregation inhibition or disassembly as a possible therapeutic approach for AD.

Methylene blue (MB), a phenothiazine compound initially used as an antiseptic and currently approved for treating methemoglobinemia, inhibits tau and Aβ aggregation *in vitro*. In a phase II clinical trial MB (Rember, TauRx Therapeutics, Singapore) significantly improved cognitive functions compared to placebo controls and slowed the progression of AD over the course of a year (47). Other compounds like anthraquinones (48) and cyanine dyes

(15) were screened for their ability to disrupt tau aggregates *in vitro* and in cell cultures.

In conclusion, AD is a clear example of how the prevailing conceptual frame regarding pathophysiology of a disease can affect the resources and efforts invested in the basic investigation and development of diagnostic and therapeutic strategies for such an important disease. Currently, there is a renewed interest in the role that tau and tau modifications may play in AD. Studies in this direction have allowed the design of new strategies for AD diagnosis with molecules that may permit the specific visualization of tau aggregates (49), along with the development of treatment strategies for AD and other tauopathies based on inhibitors of tau modification and/or aggregation.

Acknowledgments

Research was supported by a grant from Fondecyt 1080254 and the Alzheimer's Association, USA (to RBM).

References

1. Alzheimer A. A singular disorder that affects the cerebral cortex. In: Hochberg CN, Hochberg FH, eds. Neurologic Classics in Modern Translation. New York: Hafner Press;1977. pp. 41–43.
2. Maccioni RB, Concha I, Otths C, et al. The protein kinase cdk5: structural aspects, roles in neurogenesis and involvement in Alzheimer's pathology. Eur J Biochem 2001;268:1518–1529.
3. Maccioni RB, Barbeito L, Muñoz JP. The molecular bases of Alzheimer's disease and other neurodegenerative disorders. Arch Med Res 2001;32:367–381.
4. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci USA 1986;83:4044–4048.
5. Grundke-Iqbal I, Iqbal K, Tung YC, et al. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA 1986;83:4913–4917.
6. Maccioni RB, Cambiazo V. Role of microtubule-associated proteins in the control of microtubule assembly. Physiol Rev 1995;75: 835–864.
7. Rojo L, Fernandez J, Maccioni AA, et al. Neuro-inflammation: implications for the pathogenesis and molecular diagnosis of Alzheimer's disease. Arch Med Res 2008;39:1–16.
8. Fernandez J, Rojo LE, Kuljis RO, et al. The damage signal hypothesis of AD. J Alzheimers Dis 2008;14:329–333.
9. Maccioni RB, Rojo LE, Fernandez JA, et al. The role of neuroimmunomodulation in Alzheimer's disease. Ann NY Acad Sci 2009;1153: 240–246.
10. Maccioni RB, Vera JC, Dominguez J, et al. A discrete repeated sequence defines a tubulin binding domain on microtubule-associated protein tau. Arch Biochem Biophys 1989;275:568–579.
11. González-Billault C, Farías G, Maccioni RB. Modification of tau to an Alzheimer's type protein interferes with its interaction with microtubules. Cell Mol Biol 1998;44:1117–1127.
12. Farias G, Gonzalez C, Maccioni RB. Immunological characterization of epitopes on tau of Alzheimer's type and chemically modified tau. Mol Cell Biochem 1997;168:59–66.
13. Ghoshal N, García-Sierra F, Wuu J, et al. Tau conformational changes correspond to impairments of episodic memory in mild cognitive impairment and Alzheimer's disease. Exp Neurol 2002;177:475–493.
14. Maccioni RB, Lavados M, Maccioni CB, et al. Anomalously phosphorylated tau protein and Abeta fragments in the CSF of Alzheimer's and MCI subjects. Neurobiol Aging 2006;27:237–244.
15. Duff K, Kuret J, Congdon EE. Disaggregation of Tau as a therapeutic approach to Tauopathies. Curr Alzheimer Res 2010 Jan 21 [Epub ahead of print].
16. Tabaton M, Mandybur TI, Perry G, et al. The widespread alteration of neurites in Alzheimer's disease may be unrelated to amyloid deposition. Ann Neurol 1989;26:771–778.
17. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002; 297:353–356.
18. Ferreira ST, Vieira MN, De Felice FG. Soluble protein oligomers as emerging toxins in Alzheimer's and other amyloid diseases. Life 2007;59:332–345.
19. Maccioni RB, Lavados M, Maccioni CB, et al. Biological markers of Alzheimer's disease and mild cognitive impairment. Curr Alzheimers Res 2004;1:307–314.
20. Morales I, Farias G, Maccioni RB. Neuroimmunomodulation in the pathogenesis of Alzheimer's disease. Neuroimmunomodulation 2010; 17:202–204.
21. Delacourte A. The natural and molecular history of Alzheimer's disease. J Alzheimers Dis 2006;9:187–194.
22. Berger Z, Roder H, Hanna A, et al. Accumulation of pathological tau species and memory loss in a conditional model of tauopathy. J Neurosci 2007;27:3650–3662.
23. Maeda S, Sahara N, Saito Y, et al. Granular tau oligomers as intermediates of tau filaments. Biochemistry 2007;46:3856–3861.
24. Maeda S, Sahara N, Saito Y, et al. Increased levels of granular tau oligomers: an early sign of brain aging and Alzheimer's disease. Neurosci Res 2006;54:197–201.
25. Perez M, Arrasate M, Montejo de Garcini E, et al. *In vitro* assembly of tau protein: mapping the regions involved in filament formation. Biochemistry 2001;40:5983–5991.
26. Sibille N, Sillen A, Leroy A, et al. Structural impact of heparin binding to full-length tau as studied by NMR spectroscopy. Biochemistry 2006;45: 12560–12572.
27. von Bergen M, Berghorns S, Biernat J, et al. Tau aggregation is driven from a transition coil to beta sheet structure. Biochem Biophys Acta 2005;3:1739.
28. Mukrasch MD, Markwick P, Biernat J, et al. Highly turn conformations in natively unfolded tau protein identified from residual dipolar couplings and molecular simulation. J Am Chem Soc 2007;129: 5235–5243.
29. Avila J, Perez M, Lucas J, et al. Assembly in vitro of tau protein and its implications in Alzheimer's disease. Curr Alzheimers Res 2004;1: 97–101.
30. Maccioni RB. Potential clues toward Alzheimer's disease treatment. Rev Farmacol Chile 2009;2:34.
31. Jeganathan S, von Bergen M, Mandelkow EM, et al. The natively unfolded character of tau and its aggregation to Alzheimer-like paired helical filaments. Biochemistry 2008;47:10526–10539.
32. Alvarez A, Muñoz JP, Maccioni RB. A cdk5/p35 stable complex is involved in the beta-amyloid induced deregulation of cdk5 activity in hippocampal neurons. Exp Cell Res 2001;264: 266–275.
33. Otth C, Concha II, Arendt T, et al. A betaPP induces cdk5-dependent tau hyperphosphorylation in transgenic mice Tg2576. J Alzheimers Dis 2002;4:417–430.
34. Zambrano CA, Egana JT, Nunez MT, et al. Oxidative stress promotes tau dephosphorylation in neuronal cells: the roles of cdk5 and PP1. Free Radic Biol Med 2004;36:1393–1402.
35. Lavados M, Guillon M, Mujica MC, et al. Mild cognitive impairment and Alzheimer's patients display different levels of redox-active CSF iron. J Alzheimers Dis 2008;13:225–232.

36. Neumann K, Navarrete L, Rojo L, et al. Insulin resistance and Alzheimer's disease: molecular links and clinical implications. Curr Alzheimers Res 2008;5:438−447.
37. Orellana DI, Quintanilla RA, Maccioni RB. Neuroprotective effect of TNFalpha against the beta-amyloid neurotoxicity mediated by cdk5 kinase. Biochim Biophys Acta 2007;1773:254−263.
38. Schwab C, McGeer PL. Inflammatory aspects of Alzheimer's disease and other neurodegenerative disorders. J Alzheimers Dis 2008;13: 359−369.
39. Quintanilla RA, Orellana DI, Gonzalez-Billault C, et al. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. Exp Cell Res 2004;295:245−257.
40. Saez ET, Pehar M, Vargas M, et al. Production of NGF by β amyloid stimulated astrocytes induces p75NTR-dependent tau hyperphosphorylation in cultured hypocampal cells. J Neurosci Res 2006;84:1098−1106.
41. Saez ET, Pehar M, Barbeito L, et al. Astrocytic nitric oxide triggers tau hyperphosphorylation in hippocampal neurons. *In vivo* 2004;18: 275−280.
42. Leclerc E, Sturchler E, Vetter SW, et al. Crosstalk between calcium, amyloid beta and the receptor for advanced glycation endproducts in Alzheimer's disease. Rev Neurosci 2009;20:95−110.
43. Jinwal UK, Koren J, Borysov SI, et al. Hsp90 cochaperone, FKBP51, increases Tau stability and polymerizes microtubules. J Neurosci 2010;13(30):591−599.
44. Luo W, Dou F, Rodina A, et al. Roles of heat-shock protein 90 in maintaining and facilitating the neurodegenerative phenotype in tauopathies. Proc Natl Acad Sci USA 2007;104:9511−9516.
45. Noble W, Planel E, Zehr C, et al. Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration in vivo. Proc Natl Acad Sci USA 2005;102:6990−6995.
46. Le Corre S, Klafki HW, Plesnila N, et al. An inhibitor of tau hyperphosphorylation prevents severe motor impairments in tau transgenic mice. Proc Natl Acad Sci USA 2006;103:9673−9678.
47. Oz M, Lorke D, Petroianu G. Methylene blue and Alzheimer's disease. Biochem Pharmacol 2009;78:927−932.
48. Pickhardt M, Gazova Z, Bergen M, et al. Anthraquinones inhibit tau aggregation and dissolve Alzheimer's paired helical filaments in vitro and in cells. J Biol Chem 2005;280:3628−3635.
49. Rojo LE, Alzate-Morales J, Saavedra IN, et al. Selective interaction of lansoprazole and astemizole with Tau polymers: potential new clinical use in diagnosis of Alzheimer's disease. J Alzheimers Dis 2010;19: 573−589.