

Alzheimer Disease and Related Tauopathies: Possible Neuroprotective Strategies

Meketa Muñoz ^{1*}, Paul Naranjo ¹, Lakies Meerbeke¹ Faculty

of Neuroscience, Colombia

*Corresponding Author : Meketa Muñoz, Faculty of Neuroscience Colombia E-mail: Meketa@gmail.com

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Abstract

Alzheimer disease (AD) is the most common cause of dementia in adults. The current therapy for AD has only moderate efficacy in controlling symptoms, and it does not cure the disease. Recent studies have suggested that abnormal hyperphosphorylation of tau in the brain plays a vital role in the molecular pathogenesis of AD and in neurodegeneration. This article reviews the current advances in understanding of tau protein, regulation of tau phosphorylation, and the role of its abnormal hyperphosphorylation in neurofibrillary degeneration. Furthermore, several therapeutic strategies for treating AD on the basis of the important role of tau hyperphosphorylation in the pathogenesis of the disease are described. These strategies include (1) inhibition of glycogen synthase kinase-3 β (GSK-3 β), cyclin-dependent kinase 5 (cdk5), and other tau kinases; (2) restoration of PP2A activity; and (3) targeting tau O-GlcNAcylation. Development of drugs on the basis of these strategies is likely to lead to disease-modifying therapies for AD.

Keywords

Alzheimer disease, tau, neurodegeneration, GSK-3 β , cdk5, protein phosphatases, O-GlcNAcylation, therapy.

Introduction

Alzheimer disease (AD) is a chronic neurodegenerative disease that is characterized clinically by a progressive decline of cognitive function, leading to dementia. The disease eventually leads to the death of affected individuals an average of nine years after diagnosis. Approximately 27 million individuals are suffering from AD worldwide, and it accounts for the majority of cases of dementia in adults. For the last three decades, the standard treatments for AD have been acetylcholinesterase inhibitors to improve cognitive function, and other drugs to manage the mood disturbance, agitation and psychosis that often occur in the later stages of the disease. In the recent years, memantine, an NMDA (N-methyl-D-aspartate) receptor antagonist and a potentially neuroprotective agent, has been widely used. However, all of these treatments show only modest symptomatic effects. The major barrier to effective treatments is the lack of full understanding of the mechanism of AD.

Amyloid β (A β) toxicity is believed to play a primary role in the development of AD. Thus, anti-amyloid strategies have been the primary focus of AD drug development for the last 10 years. Recently, more and more evidence has demonstrated a crucial role of tau abnormalities in AD neurodegeneration, suggesting that tau could be a promising therapeutic target for developing disease-modifying drugs of AD. In this article, we first describe tau protein and the tau abnormalities involved in AD, followed by the molecular mechanism of neurofibrillary degeneration. Then, we discuss the therapeutic strategies that are based on reversal of abnormal hyperphosphorylation of tau.

Tau Protein

Tau was first discovered as a microtubule-associated protein (MAP) that stimulates tubulin assembly into microtubules in the brain. There was not much research interest in tau protein until a decade later, when it was found to make up the paired helical filaments (PHFs) of NFTs in AD brain.

Human tau gene is located on the long arm of chromosome 17 (position 17q21) and was found to contain 16 exons. This single tau gene encodes six tau isoforms in adult human brain as a result of alternative splicing of its mRNA. The six tau isoforms differ from each other by the presence or absence of one or two inserts (29 or 58 amino acids) in the N-terminal part and by the presence of either three or four repeats in the C-terminal half. The N-terminal inserts are highly acidic. The repeats in the C-terminal half of tau are the domains by which tau binds to microtubules.

Tau Mutations Found in Frontotemporal Dementia Promote Abnormal Hyperphosphorylation

Tau mutations, which cause FTDP-17, result either in increase in 4-R: 3-R tau ratio or in missense mutations in the protein. Both 4-repeat tau and the mutated protein are more easily abnormally hyperphosphorylated than the normal wild-type protein. Four of these missense mutations, G272V, P301L, V337M, and R406W, which have been most extensively studied to date, make tau a more favorable substrate than the wild-type protein for abnormal hyperphosphorylation by brain protein kinases in vitro.

Tau phosphorylation and Alzheimer's disease pathophysiology

Although increasing evidence suggests that tau has roles in the cell beyond its ability to regulate microtubule dynamics, the phosphorylation-regulated function of tau remains of primary interest in studies assessing the potential pathophysiological role of the protein in AD and other tauopathies (for a review, see reference). Studies have clearly demonstrated that tau phosphorylation at various sites, by many different kinases, regulates the microtubule affinity of the protein, as well as its ability to regulate microtubule dynamics, and reviewed in reference. Phosphorylation of tau by GSK3 β and Cdk5 affects tau-microtubule interactions by reducing the microtubule affinity of tau; phosphorylation of Ser²¹⁴ by PKA has also been demonstrated to have a similar effect.



Most notably, phosphorylation of the serines within the Lys-Xaa-Gly-Ser (KXGS) motifs (and particularly at the 12E8 [Ser²⁶²/Ser³⁵⁶] site) of the microtubule-binding domains (MTBDs) of tau consistently exerted a strong negative effect on tau-microtubule interactions; a prominent kinase that phosphorylates the KXGS motif is MARK [1]. A recent structural study of pseudo-phosphorylated tau indicated that phosphorylation at the KXGS motif introduces a destabilizing rigid turn to three residues adjacent to Ser²⁶² that decouples tau from microtubules. Given these and other findings, it is reasonable to speculate that the hyperphosphorylation of tau may contribute to the reported defects of microtubule integrity in AD brains.

Results

Systemic administration of streptozotocin (STZ), a compound that is selectively toxic toward insulin-producing β -cells in the islets of Langerhans, is often used to induce diabetes in rodent models of disease. In wild-type mice, peripheral administration of STZ led to increased tau phosphorylation at various sites, but did not lead to the formation of insoluble aggregates. In a mouse model expressing FTDP-17 tau, a similar treatment paradigm exacerbated tau pathology, including increasing the levels of AT8 immunoreactivity, dystrophic neurites and NFTs. The mechanism responsible for the increase in tau phosphorylation in response to insulin deficiency is unlikely to be elevated GSK3 β activity (in fact, a decrease in the active form of the kinase was observed); instead, the specific inactivation of protein phosphatase 2A (PP2A) may be responsible. One potential mechanism for STZ-induced reduction of PP2A activity is through the induction of hypothermia. Interestingly, anesthesia-induced hypothermia also results in increases in tau phosphorylation through the inhibition of phosphatase activity.

Central administration of STZ has been proposed to induce AD, as this agent induces behavioral and neuropathological changes that recapitulate the disease phenotype. Although the mechanism of action of centrally administered STZ differs from that observed when the compound is administered systemically, central administration of STZ results in reduced levels of both the insulin receptor and insulin in the brain. In a recent study, STZ injected directly into the cerebral ventricles resulted in acute increases in tau phosphorylation at AD-related epitopes, as well as the expected increase in the levels of activated GSK3 β .

Conclusion

In conclusion, the abnormal hyperphosphorylation of tau seen in AD is different from the normal and from the transient hyperphosphorylation of this protein that occurs during development, anesthesia, or hypothermia. The cytosolic AD abnormally hyperphosphorylated tau (AD P-tau) is sedimentable/oligomeric, and probably causes neurodegeneration by sequestering normal MAPs and disrupting microtubule network. Tau mutations found in frontotemporal dementia may cause neurodegeneration through promoting abnormal hyperphosphorylation of tau. AD P-tau self-assembles into PHF/SF, forming neurofibrillary tangles. Tau truncation found in AD brain promotes its self-assembly into PHF/SF. Unlike AD P-tau, PHF/SF neither sequester normal MAPs nor disrupt microtubules. Thus, inhibition of abnormal hyperphosphorylation of tau offers a promising therapeutic target for AD and related tauopathies.

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