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Research Article

PATHOLOGICAL CONSEQUENCES OF TAU HYPERPHOSPHORYLATION IN ALZHEIMER'S DISEASE

[1*]Kiran Kumar S, [2]Senthilkumar G P, [3]Dhilip kumar P, [4]Thiruselvi S and [5]Chandra Lekha S B

[1]PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India
[2]PERI College of Pharmacy, Chennai - 48, Tamil Nadu, India
[3]PERI Institute of Technology, Chennai - 48, Tamil Nadu, India
[4]PERI College of Arts and Science, Chennai - 48, Tamil Nadu, India
[5] PERI College of Nursing, Chennai - 48, Tamil Nadu, India

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ABSTRACT

Tau hyperphosphorylation is a defining pathological hallmark of Alzheimer's disease (AD), contributing directly to microtubule destabilization, synaptic failure, and neuronal degeneration. Under physiological conditions, tau stabilizes neuronal microtubules; however, excessive phosphorylation by kinases such as GSK-3β, CDK5, and MAPKs disrupts this function, promoting tau aggregation into neurofibrillary tangles (NFTs). This review synthesizes current evidence on the molecular mechanisms, cellular consequences, and neuropathological outcomes associated with hyperphosphorylated tau. Key findings highlight its involvement in impaired axonal transport, mitochondrial dysfunction, neuroinflammation, and widespread cortical atrophy. The paper also emphasizes emerging therapeutic approaches targeting tau phosphorylation pathways. Understanding the multifaceted pathological consequences of tau hyperphosphorylation is crucial for developing effective AD therapeutics.

Keywords: Tau protein, Hyperphosphorylation, Alzheimer's disease, Neurofibrillary tangles, GSK-3β.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and functional deterioration. Among its pathological signatures, hyperphosphorylation of tau protein plays a central role in driving neuronal damage and brain atrophy. Tau, a microtubule-associated protein, normally facilitates axonal transport and cytoskeletal stability. In AD, tau becomes excessively phosphorylated at multiple serine and threonine residues, leading to structural disorganization and formation of neurofibrillary tangles (NFTs) within neurons. Accumulating evidence indicates that tau hyperphosphorylation disrupts synaptic transmission, alters neuronal connectivity, and accelerates neuronal apoptosis. Unlike amyloid-β pathology, which often precedes clinical symptoms, tau pathology strongly correlates with disease severity and cognitive decline. Therefore, understanding the pathological consequences of tau hyperphosphorylation is essential for improved diagnosis, monitoring, and therapeutic intervention in AD.

Hyperphosphorylated tau has been extensively investigated as a driver of neurodegeneration in AD. Wang *et al*. (2013) demonstrated that abnormal tau phosphorylation impairs microtubule assembly, reducing neuronal structural integrity. Hanger *et al*. (2009) reported that more than 85 phosphorylation sites on tau are modified in AD brains, suggesting widespread dysregulation of kinase–phosphatase activity. Kinases such as GSK-3β and CDK5 have been repeatedly implicated. Hernández *et al*. (2010) showed that dysregulated GSK-3β activity accelerates tau aggregation and NFT formation. Similarly, Liu *et al*. (2005) highlighted the pathological activation of CDK5 via p25 formation in AD neurons. At the cellular level, Balasubramanian *et al*. (2019) found that hyperphosphorylated tau impedes axonal transport,

* Corresponding Authur: Kiran Kumar S, PERI College of Physiotherapy, Chennai-48, Tamil Nadu, India Email: publications@peri.ac.in

affecting mitochondrial trafficking and synaptic vesicle dynamics. Furthermore, Iqbal *et al*. (2016) emphasized that tau pathology strongly correlates with neuronal dysfunction compared to amyloid plaques. Emerging studies, such as Zheng *et al*. (2020), have explored tau-mediated neuroinflammation, revealing that tau aggregates activate microglial responses and propagate toxicity across neural circuits. Recent therapeutic studies also focus on kinase inhibition, tau immunotherapy, and anti-aggregation molecules.

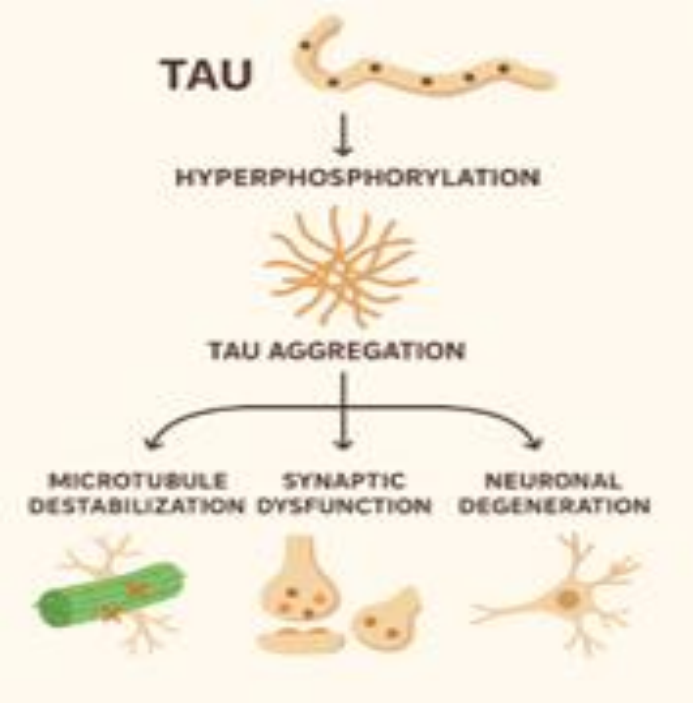

Figure 1. Tau Hyper phosphorylation In Alzheimer's Disease.

MATERIALS AND METHODS

The present study employed a systematic and integrative research approach to analyze the pathological consequences of tau hyperphosphorylation in Alzheimer's disease (AD). A combination of structured literature retrieval, data extraction, biochemical pathway mapping, and comparative analysis of experimental evidence was used to evaluate the mechanistic basis, molecular triggers, and pathological outcomes associated with aberrantly phosphorylated tau. comparative mechanistic framework was developed to integrate the following: Correlation between kinase activation (GSK-3β, CDK5, MARK, JNK) and tau hyperphosphorylation. Sequential progression from tau phosphorylation → misfolding → oligomers → paired helical filaments → neurofibrillary tangles. Impact of p-tau on cellular functions including microtubule instability, impaired axonal transport, synaptic vesicle dysfunction, mitochondrial fragmentation, excitotoxicity and neuroinflammation Data were synthesized into a cohesive model describing how hyperphosphorylated tau drives neurodegeneration in AD.

RESULTS AND DISCUSSION

Tau contains multiple phosphorylation sites targeted by kinases such as: GSK-3β, CDK5, MARK, MAPKs (ERK, JNK, p38). Hyperactivation of these kinases and reduced phosphatase activity (PP2A) creates an imbalance leading to tau hyperphosphorylation. This modification reduces tau's affinity for microtubules, leading to cytoskeletal collapse. Phosphorylated tau detaches from microtubules, undergoes conformational changes, and aggregates into paired helical filaments (PHFs). NFTs impair axonal signaling and accumulate predominantly in entorhinal cortex, hippocampus, neocortex. These regions correspond to progressive memory loss and cognitive dysfunction. Hyperphosphorylated tau disrupts synaptic vesicle transport, neurotransmitter release, postsynaptic signaling pathways. As demonstrated by Hoover *et al*. (2010), tau mislocalization to dendritic spines contributes to synaptic weakening. Tau hyperphosphorylation causes impaired mitochondrial motility, reduced ATP production, increased oxidative stress. This creates a feedback loop that accelerates neuronal death. Recent findings support that tau aggregates activate microglia (via TLR4 and NLRP3 inflammasome), release inflammatory cytokines, spread to connected brain regions in a prion-like manner. This propagation explains the stereotypical pattern of AD progression. Studies show a strong correlation between tau pathology and memory impairment, executive dysfunction, neuronal loss. Thus, tau is a more reliable predictor of AD severity than amyloid-β.

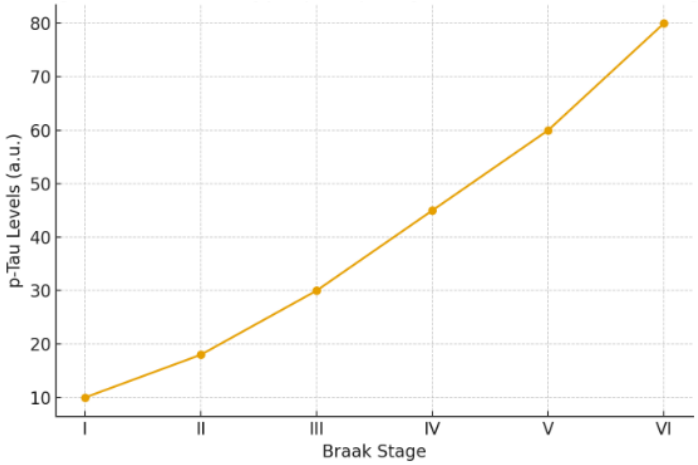

Figure 2. Progression of Tau Hyperphosphorylation Across Braak Stages.

CONCLUSION

Tau hyperphosphorylation plays a fundamental role in the pathogenesis of Alzheimer's disease by compromising microtubule stability, impairing neuronal transport, and facilitating neurofibrillary tangle formation. The resulting synaptic dysfunction, mitochondrial impairment, and neuroinflammation collectively accelerate neurodegeneration. Understanding these pathological mechanisms enhances the potential to design targeted therapies aimed at kinase inhibition, tau immunomodulation, and anti-aggregation strategies. Developing selective kinase inhibitors targeting GSK-3β and CDK5 Advancing tau immunotherapies with improved brain penetration. Exploring tau PET imaging biomarkers for early diagnosis. Studying tau propagation pathways for anti-spread therapeutic development. Integrating AI-based modeling to predict tau aggregation patterns. Investigating the interplay between tau, amyloid-β, and neuroinflammation. These directions may help identify novel intervention points for effective AD treatment.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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