International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 3 | May – Jun 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i3.14

The Role of Phosphorylated-Tau 181 in Enhancing Neuroplasticity After Ischemic Stroke

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ABSTRACT

Ischemic stroke is a predominant cause of neurological impairment globally. Notwithstanding progress in acute treatment, the long-term functional recovery of individuals continues to be constrained. Recent research has concentrated on the function of neurodegenerative biomarkers, particularly phosphorylated tau 181 (p-tau 181), in influencing neuroplasticity following ischemic stroke. This study seeks to investigate the function of p-tau 181 in augmenting neuroplasticity following ischemic stroke. This investigation was performed by literature analysis and examination of experimental data from animal models and human subjects. The findings indicated that p-tau 181 levels were markedly elevated during the subacute phase post-stroke and correlated with the reconfiguration of brain circuits facilitating the recovery of motor and cognitive functioning. The mechanisms involved encompass enhanced synaptic connection, the induction of neurogenesis, and augmented myelination. While p-tau 181 is frequently linked to the neurodegenerative mechanisms of Alzheimer's disease, in the setting of stroke, the transient elevation of p-tau 181 seems to serve an adaptive function to facilitate recovery. These findings create new prospects for the advancement of biomarker-driven therapy techniques to enhance post-stroke recovery. Nonetheless, additional investigation is required to comprehend the physiological and pathological thresholds of p-tau 181 and its possible long-term implications.

Keywords: phosphorylated-tau 181; neuroplasticity; ischemic stroke.

INTRODUCTION

An ischemic stroke is defined by the interruption of cerebral blood flow, resulting in neuronal necrosis and functional deficits.[1] Notwithstanding progress in acute stroke treatment, numerous survivors endure lasting neurological impairments owing to the restricted regenerating potential of the adult central nervous system (CNS). The brain has intrinsic neuroplasticity mechanisms that provide partial functional recovery by reorganizing neural pathways structurally and functionally.[2] Tau protein, recognized chiefly for its function in maintaining neuronal microtubules, has garnered interest for its participation in several physiological and pathological processes, including neuroplasticity following damage.[3] The phosphorylated variant of tau at threonine 181 (p-tau 181) has surfaced as a putative regulator of neuroplasticity subsequent to ischemic stroke.[4] Historically regarded as a harmful indicator in neurodegenerative disorders such as Alzheimer's disease, current findings indicate that p-tau 181 may have advantageous effects in stroke recovery by facilitating axonal development, dendritic remodeling, synaptic plasticity, and neurogenesis.[5]

This study seeks to consolidate the existing knowledge regarding p-tau 181's function in post-ischemic stroke neuroplasticity, examining the molecular pathways by which it may affect neuronal survival, synaptic remodeling, and functional recovery. We investigate the molecular underpinnings of p-tau 181-induced neuroplasticity, analyze the temporal and spatial patterns of p-tau 181 expression post-stroke, and evaluate novel therapeutic approaches aimed at p-tau 181 to enhance functional recovery.

Tau Protein: Structure and Function in Normal and Pathological Conditions

Tau is a microtubule-associated protein primarily expressed in neurons, where it plays essential roles in stabilizing microtubules, facilitating axonal transport, and maintaining neuronal integrity.[4] In the adult human brain, tau exists in six isoforms resulting from alternative splicing of the MAPT gene. The protein's function is tightly regulated by post-translational modifications, with phosphorylation being the most extensively studied due to its implications in both normal physiology and pathological conditions. Under physiological conditions, tau phosphorylation is a dynamic process that modulates the protein's affinity for microtubules, thereby influencing cytoskeletal stability and plasticity. This regulated phosphorylation is crucial for normal neuronal development, axonal growth, and synaptic function.[5,6] Recent evidence suggests that controlled tau phosphorylation may also facilitate adaptive responses to cellular stressors, potentially serving as a protective mechanism in specific contexts.

In neurodegenerative disorders like Alzheimer's disease, aberrant hyperphosphorylation of tau results in its detachment from microtubules, the creation of paired helical filaments, and aggregation into neurofibrillary tangles, which contributes to neuronal malfunction and demise.[7] This pathogenic tau hyperphosphorylation transpires at various locations, including threonine 181, serine 202/threonine 205 (identified by the AT8 antibody), and threonine 231.[8]

Ischemic stroke has been demonstrated to provoke tau hyperphosphorylation via pathways related to excitotoxicity, oxidative stress, and the deregulation of kinase and phosphatase activity.[9] The pattern, timing, and functional outcomes of stroke-induced tau phosphorylation seem to diverge from those seen in neurodegenerative tauopathies, indicating context-specific functions for phosphorylated tau species in various clinical situations.

P-TAU 181 IN ISCHEMIC STROKE: FROM BIOMARKER TO POSSIBLE MEDIATOR OF RECOVERY

Clinical Evidence: P-tau 181 as a Prognostic Indicator of Post-Stroke Outcomes

Recent clinical research has produced unexpected results concerning the association between p-tau 181 and cognitive outcomes following a stroke. A longitudinal study conducted by Huang et al. monitored 136 individuals experiencing their first acute ischemic stroke over a 12-month period, evaluating cognitive performance and measuring several blood biomarkers, including plasma p-tau 181. In contrast to anticipated outcomes related to the protein's involvement in neurodegenerative disorders, elevated acute plasma p-tau 181 levels correlated with a markedly reduced risk of post-stroke cognitive impairment (PSCI) at both 3 months (OR = 0.62, 95% CI = 0.40–0.94, p = 0.0243) and 12 months (OR = 0.69, 95% CI = 0.47–0.99, p = 0.0443) following a stroke. This protective connection persisted even after controlling for traditional risk variables and imaging biomarkers, indicating an independent influence of p-tau 181 on cognitive outcomes. This study posits that tau phosphorylation at threonine 181 may enhance its association with exosomes and promote the release of surplus tau,[10] suggesting a potential mechanism by which p-tau 181 could confer advantageous benefits in the post-stroke brain. Chi et al. reported analogous findings, noting that plasma p-tau 181 levels at 3 months post-stroke predicted improved cognitive outcomes at 1 year, thereby reinforcing the hypothesis that this particular tau phosphorylation event may play a role in adaptive rather than solely pathological processes following ischemic injury.[11]

Empirical Evidence: p-tau 181 and Neuronal Viability

Experimental studies have commenced to clarify the molecular pathways by which p-tau 181 may affect neuronal survival and recovery following ischemia injury. Unlike other phosphorylation sites like Thr231, which is linked to neurotoxic consequences when phosphorylated in the cis configuration,[12] phosphorylation at Thr181 seems to activate other signaling pathways that may enhance neural resilience during stress situations. In vitro investigations utilizing oxygen-glucose deprivation (OGD) models of ischemia have shown that the regulated activation of tau phosphorylation can mitigate excitotoxic neuronal death by influencing glutamate receptor trafficking and calcium homeostasis.[13,14] The neuroprotective effect was nullified when phosphorylation at this particular site was inhibited, underscoring the site-specific characteristics of tau's functional effects.

MOLECULAR MECHANISMS LINKING P-TAU 181 TO NEUROPLASTICITY

P-tau 181 and Exosome-Mediated Signaling

A significant mechanism connecting p-tau 181 to increased neuroplasticity is its interaction with exosomes, which are tiny extracellular vesicles essential for intercellular communication. Avila et al. posited that phosphorylation at Thr181 enhances tau binding to exosomes, thereby facilitating the clearance of surplus tau and boosting the release of neuroprotective substances.[6] Besides its influence on synaptic plasticity and cytoskeletal reorganization, exosomal p-tau 181 contributes to the recruitment of neural stem cells (NSCs) to the injury site. This process is crucial for the brain's self-repair capabilities after a stroke. Exosomes containing p-tau 181 can activate signaling pathways, including PI3K/Akt and MAPK/ERK, which are implicated in cell survival, neuroprotection, and stem cell proliferation.[15,16] These pathways facilitate the recruitment of endogenous neural progenitors, which can develop into neurons and glial cells, so assisting in the restoration of brain function. Moreover, exosomal p-tau 181 may augment the neurogenic capacity of stem cells by promoting the expression of genes associated with neuroplasticity and cellular resilience, thus fostering a more conducive environment for functional recovery. The recruitment and activation of NSCs constitute a vital mechanism via which p-tau 181 may facilitate post-stroke healing.

P-tau 181 significantly influences neuroplasticity by affecting cytoskeletal dynamics. Tau is a microtubule-associated protein that stabilizes microtubules in neurons, crucial for axonal transport and cellular activity. Phosphorylation of tau, particularly at the Thr181 locus, can modify its binding affinity for microtubules, resulting in instability and aggregation. Tau aggregation is typically linked to neurodegenerative disorders; however, regulated phosphorylation of tau at particular locations, such as Thr181, may promote cytoskeletal remodeling crucial for neuroplasticity. Research indicates that p-tau 181 affects dendritic spine remodeling, a crucial mechanism in the establishment of new synaptic connections following neurological damage.[17,18] This type of remodeling is especially important in brain regions impacted by ischemia injury, where the reestablishment of synaptic connection is essential for functional recovery.

P-tau 181 and BDNF Signaling

Brain-derived neurotrophic factor (BDNF) is an essential mediator of neuroplasticity, facilitating neuronal survival, synaptic plasticity, and functional recovery following brain injury. Recent research indicates a complicated interaction between p-tau 181 and BDNF signaling pathways in relation to ischemic stroke.

The BDNF and its receptor, tropomyosin receptor kinase B (TrkB) pathway is recognized for its critical function in enhancing neuronal survival, stimulating dendritic development and differentiation, and aiding synaptic recovery in the peri-infarct region.[19] Elevated BDNF levels following a stroke activate the TrkB receptor, subsequently triggering intracellular signaling cascades, including PI3K/Akt and MAPK/ERK. The PI3K/Akt pathway is recognized for inhibiting the activity of GSK-3β, a crucial enzyme in tau phosphorylation. In the realm of post-stroke neuroplasticity activation, the regulation of GSK-3β is crucial, as the equilibrium between its activation and inactivation dictates whether tau phosphorylation is pathological or adaptive,[20] thereby facilitating the reorganization of the microtubule cytoskeleton essential for the establishment of new synaptic connections and the restoration of cognitive function. The synergistic interaction between p-tau 181 and BDNF signaling may be especially significant during the subacute and chronic stages of stroke recovery when neuroplastic processes like axonal sprouting, synaptogenesis, and functional network reorganization are essential for the restoration of lost functions. By augmenting BDNF-mediated trophic support, p-tau 181 may promote these adaptive responses and improve functional recovery.

CLINICAL IMPLICATIONS AND THERAPEUTIC POTENTIAL

P-tau 181 as a Biomarker for Tailored Stroke Management

The correlation between p-tau 181 levels and post-stroke outcomes indicates its usefulness as a biomarker for risk classification and individualized treatment strategies. Individuals exhibiting decreased acute p-tau 181 levels may possess an elevated risk for cognitive impairment and could gain from enhanced cognitive rehabilitation and neuroprotective strategies.[10] Furthermore, tracking fluctuations in p-tau 181 levels over time may yield critical insights into active neuroplastic processes and recovery potential, so informing the timing and intensity of rehabilitation interventions. The advancement of highly sensitive assays for quantifying plasma p-tau 181, including single-molecule array (Simoa) technology, has rendered such monitoring progressively attainable in clinical environments.[8]

Therapeutic Approaches Targeting p-tau 181

In light of the evolving comprehension of p-tau 181's function in neuroplasticity, various treatment strategies designed to utilize or amplify its advantageous effects are currently under investigation:

(1) Small molecule modulators

Compounds that specifically enhance tau phosphorylation at Thr181 while avoiding pathological hyperphosphorylation at other locations give a viable strategy. Preclinical investigations have discovered multiple candidates exhibiting neuroprotective properties in Alzheimer's disease and other tauopathies.[21]

(2) Exosome-based therapies

Engineered exosomes loaded with p-tau 181 or compounds that augment their exosomal loading are being formulated as prospective therapeutics to facilitate neuroplasticity following a stroke. These exosomes can be engineered to specifically target cell types in the ischemic brain, thereby optimizing therapeutic efficacy and reducing off-target consequences.[22]

(3) Combined approaches with BDNF

Considering the synergistic interaction between p-tau 181 and BDNF signaling, treatments that concurrently address both pathways may prove especially efficacious. These may encompass p-tau 181 modulators combined with BDNF mimetics or strategies that augment endogenous BDNF synthesis, such as exercise or non-invasive brain stimulation.[10,23]

(4) Immunotherapeutic approaches

Antibodies that specifically identify and regulate the activity of p-tau 181, while preserving its advantageous effects, are under development as prospective treatments for stroke. These antibodies may be engineered to augment p-tau 181's engagement with particular binding partners implicated in neuroplasticity while inhibiting any possible pathological aggregation. Three primary anti-tau methods are recognized: avoiding aberrant tau phosphorylation, limiting tau aggregation, and enhancing the clearance of tau aggregates. At present, the majority of anti-tau medicines undergoing clinical trials are immunotherapeutic interventions. Following the initial revelation of tau immunotherapy's efficacy in the JNPL3 mouse model in 2007, many active vaccines, including AADvac1 and ACI-35, as well as passive immunotherapeutic antibodies such as semorinemab, gosuranemab, and BIIB076, have been developed in recent years. All exhibit substantial therapeutic effects in animal models of Alzheimer's disease. Tau immunogens combined with moderate adjuvants effectively reduce pathogenic tau levels without provoking significant unfavorable immune responses. Nonetheless, the advancement of tau antibodies lags behind that of Aβ, and none of these medicines have progressed to phase III trials.[24]

CHALLENGES AND FUTURE DIRECTIONS

Equilibrating Advantageous and Adverse Effects

A fundamental issue in targeting p-tau 181 for therapeutic applications is differentiating its advantageous effects on neuroplasticity from its possible role in long-term tau disease. The correlation between acute post-stroke tau phosphorylation and the ensuing neurodegenerative alterations is not fully elucidated, and therapies aimed at increasing p-tau 181 levels or activity must judiciously weigh immediate advantages against possible long-term hazards. Subsequent research ought to concentrate on delineating the temporal and spatial dimensions whereby p-tau 181 manifests advantageous vs adverse impacts, in addition to finding supplementary elements that affect this equilibrium. This understanding will be essential for developing treatment strategies with optimal risk-benefit ratios.

Incorporating p-tau 181 into Comprehensive Stroke Recovery Frameworks

Although the evidence supporting p-tau 181's involvement in neuroplasticity is persuasive, successful stroke recovery treatments will probably necessitate comprehensive approaches that consider other elements of the post-stroke milieu. Future investigations should examine the best integration of p-tau 181-targeted therapy with additional neuroprotective and neurorestorative strategies, including anti-inflammatory medicines, neurotrophic support, and rehabilitation methodologies. The relationship between p-tau 181 and other post-stroke variables, including inflammation, oxidative stress, and vascular remodeling, requires additional examination. A deeper comprehension of these intricate relationships will enable the formulation of multiple treatment regimens that encompass the entire range of healing mechanisms.

CONCLUSION

Recent findings about p-tau 181's function in post-stroke neuroplasticity signify a transformative change in our comprehension of tau phosphorylation in acute cerebral damage. P-tau 181 is not only an indicator of illness; it actively contributes to adaptive responses that enhance neuronal survival, facilitate synaptic remodeling, and support functional recovery following ischemic stroke. P-tau 181 fosters a milieu that promotes neuroplastic alterations essential for functional enhancement through its interactions with exosome-mediated signaling, BDNF pathways, and synaptic plasticity processes. This comprehension facilitates novel opportunities for therapeutic intervention, encompassing prospective methods such as small chemical modulators, modified exosomes, and immunotherapeutic techniques.

Nonetheless, considerable obstacles persist in converting these findings into efficacious clinical interventions. The intricate temporal dynamics of p-tau 181's impacts, the necessity to reconcile advantageous neuroplastic functions with possible long-term pathological contributions, and the amalgamation of p-tau 181-targeted methodologies with alternative stroke recovery strategies necessitate additional research.

Future research in this domain offers the potential for creating innovative therapeutics that utilize the neuroplasticity-enhancing characteristics of p-tau 181 to enhance outcomes for stroke survivors. By further clarifying the molecular processes by which this particular tau phosphorylation event affects recovery, we advance toward a more thorough comprehension of post-stroke neuroplasticity and more effective strategies for its enhancement.

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