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REVIEW ARTICLE **OPEN ACCESS**

Unveiling the Role of GSK-3β as a Prominent Mediator of Neuroinflammation in Parkinson's Disease

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ABSTRACT

Neuroinflammation, characterized by detrimental effects on brain neurons, assumes a pivotal role in driving the advancement of neurodegenerative conditions, like Alzheimer's disorder and Parkinson's ailment (PD). The physiological immune system serves as the initiating factor for inflammatory response within cells and the organism. Glial cells and astrocytes orchestrate an immune response to address cellular physiological changes temporarily, however the Persistent triggering results in pathological advancement. Extensive research indicates that certain proteins, including NLRP3, GSK-3β, PPARγ, TNF, and NF-κB alongside other mediatory proteins, are involved in mediating this inflammatory response. The NLRP3 inflammasome represents a prominent initiator of neuroinflammatory reactions; however, the regulatory mechanisms governing its activation and the cross-talk with various inflammatory mediators remain poorly understood. Emerging data propose GSK-3β's involvement in controlling NLRP3 activation; nevertheless, the precise underlying mechanistic pathogenesis by which GSK-3β influences this process remains to be fully elucidated. This comprehensive review seeks to elucidate the complex interactions between inflammatory markers, the neuroinflammation progression mediated by GSK-3β, and their correlations with regulatory transcription factors and posttranslational protein modifications. Furthermore, recent advancements in clinical therapeutic interventions aimed at these proteins are explored, providing an in-depth overview of the advancements in managing PD, while highlighting the existing gaps in knowledge in this area of research.

KEYWORDS: *GSK-3β-mediated neuroinflammation, Parkinson's disease, GSK-3: Glycogen synthase kinase 3*

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INTRODUCTION

Parkinson's disease (PD) is a second most common progressive and incapacitating neurodegenerative condition worldwide that predominantly targets the elderly demographic. PD, first described by James Parkinson in 1817 as "shaking palsy," is characterized by a progressive degradation of connections between dopaminergic neurons in the substantia nigra region of the brain, leading to diverse motor and non-motor symptoms[1]. Motor manifestations of PD consist of bradykinesia, rigidity, and tremors, whereas non-motor features involve excessive drooling, a mask-like facial expression, gait disturbances, sleep disturbances, and leg restlessness. In the absence of appropriate treatment, individuals with PD encounter heightened rigidity and cognitive impairment during physical activities thereby predisposing them to challenges like aspiration pneumonia and pulmonary embolism, ultimately augmenting the risk of mortality[2]. Globally, PD affects approximately 1-2 individuals per 1000 people, with a prevalence of 0.58 million among the Indian population based on demographic data recorded in 2016[3]. Limited therapeutic and diagnostic strategies pose challenges in effectively managing PD, leading to an expected rise in its prevalence in the future. Notably, genetic predisposition, aging, environmental pollution, and lifestyle choices emerge as significant contributing elements in PD pathogenesis[4].

PD is characterized by lewy body accumulation and dopaminergic neuron loss in the midbrain's substantia nigra pars compacta (SNpc), resulting in impaired motor activities and coordination due to deficient dopamine (DA) in the striatum. Additionally, PD progression is influenced by neuroinflammatory responses, protein misfolding disorders, oxidative stress, and disrupted organelle function[5].

Neuroinflammation is receiving significant attention as a contributing element to the advancement of PD. Notably, glycogen synthase kinase-3 (GSK-3) has emerged as a primary inflammatory mediator during microglial activation. GSK-3, a versatile protein kinase primarily found in the brain, participates in various cellular activities such as differentiation, protein synthesis, glycogen metabolism, immune responses, and cell death[6]. Moreover, GSK-3 plays a central role in multiple signalling pathways regulated through Wnt/β-catenin, insulin, insulin receptor, insulin-like growth factor, nuclear factor κB (NF-κB), and transforming growth factor-β (TGF-β) signaling pathways[7]. Through its influence on cellular balance of oxidative stress, maintenance of protein homeostasis, and regulation of transcription factors, GSK-3 significantly impacts the progression of PD [8].

Moreover, glial cells, in addition to neuronal alterations, contributes in neuroinflammatory processes associated with neurodegeneration. Studies on postmortem PD brains have revealed overexpression of GSK-3β activity in the striatum and the presence of phosphorylated GSK-3β within the Lewy body aggregates [9]. Recent research has also identified links between mitochondrial dysfunction and neurodegenerative progression, leading to the emergence of therapeutic strategies targeting mitochondrial dyshomeostasis[10]. Furthermore, inflammasomes, including NLRP3, NLRP1, NLRC4, and AIM2, which are integral to the inflammatory process, have been implicated in PD pathogenesis, particularly NLRP3 [11].

INFLAMMATION AND IMMUNITY IN PD

Inflammation and immune responses play a crucial role in PD, which is traditionally recognized as a movement disorder. The contemporary perspective on PD recognizes its multifactorial complexity, as it involves the controlling centres of human brain, associated with complex interplay of diverse pathological triggers. The underlying pathology of PD remains incompletely elucidated; however, it encompasses intricate signaling cascades involving oxidative damage, endoplasmic reticulum (ER) stress, inflammation, and immune responses, especially associated with aging and proteinopathy, emerging as a significant contributing factor and extensive research to unravel its mechanistic contribution to the advancement of neurodegenerative conditions [12].

The pathogenesis of PD entails the initiation and progression of neuroinflammation, driven by the activation of microglia-mediated inflammasome assembly. Inflammasomes function as intracellular receptors and sensors, and among them, NLRP3 plays a crucial role as a pattern recognition receptor (PRR) expressed in macrophages[13]. In the past decade, research efforts have underscored the substantial involvement of NLRP3 in neuroinflammatory processes, where it interacts with both the innate immune system and caspase-1, an apoptotic protein[14]. NLRP3 is responsible for recognizing damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), thereby triggering downstream inflammatory pathways. The outcome of this activation can either regulate the inflammatory response under normal circumstances or intensify inflammation in pathological conditions[15]. In its structure, NLRP3 consists of three distinct domains: an amino-terminal pyrin domain, a central nucleotide-binding and oligomerization domain (NOD), and a carboxyl-terminal leucine-rich repeat domain (LRR)[16]. The formation of the NLRP3 inflammasome results in the release of potent proinflammatory cytokines, which contributing to the process of neurodegeneration. The initial defense mechanism in response to detrimental triggers within the body involves inflammation controlled by the immune response. A well-balanced response is protective, but an uncontrolled response can lead to the development of cellular pathology. In the presence of pathological triggers, the innate immune system is activated, particularly microglia-mediated innate immunity in the CNS, leading to neuroinflammation[17].This mechanism is aided by astrocytes and invading macrophages, and activation of the inflammasome due to neuronal damage. Cytokines and chemokines secreted by glial cells catalyse this process. The production of Cytokine occurs in two stages: initial phase encompasses the secretion of proinflammatory cytokines while the second phase involves the generation of anti-inflammatory cytokines. Both phases contribute to counterbalancing the inflammatory process to prevent sustained damage caused by inflammation [18].

Peripheral macrophages are pivotal in inflammatory processes, yet microglia, which are macrophages residing in the brain, maintain preliminary homeostasis. The equilibrium between inflammatory and anti-inflammatory actions is upheld by the interplay of various factors as activation of M1 and M2 microglia[19]. M1 microglia produce inflammatory factors primarily mediated by toll-like receptors (TLRs), while M2 microglia, acting as healers and scavengers, secrete IL-10 and IL-4. Upon interaction with α-Syn aggregates, microglia exhibit accelerated secretion of proinflammatory mediators, leading to neuronal death under excessive activity. However, restrained activation of microglia results in the production of neurotrophic factors that serve as a protective mechanism in neurons[20][21]. PD patients display augmented infiltration of T and B cells in the SNpc, alongside increased levels of M1-associated cytokines, such as TNF-α and IL-6, and an enhanced presence of MHCII-positive cells. These alterations are strongly associated with the advancement of PD, particularly concerning α-Synuclein aggregation [22]. Furthermore, the configuration of peripheral benzodiazepine receptors on the external mitochondrial membrane of

microglia and macrophages undergoes changes within the Parkinson's disease (PD) brain. The activation of the M2 phenotype becomes noticeable in chronic disease situations and entails engagement with α-Synuclein, though the exact mechanism underlying M2 microglial participation in PD still requires comprehensive clarification. The interplay between M1 and M2 microglia is of paramount importance in the progression of neuroinflammation-mediated disease [23].

In addition to microglia, astrocytes play a substantial role in neuroinflammation. Clinical observations reveal astrogliosis in PD brains, this observation is consistent with preclinical PD models. Reactive astrogliosis is characterized by enlarged cell bodies and processes, accompanied by increased expression of glial fibrillary acidic protein (GFAP[24]). Astrocytes cooperate with microglia to amplify inflammatory signals with microglial-derived inflammatory mediators serving as stimuli for astrocytes. The phenomenon of neuroinflammation extends beyond the CNS to PNS, and both systems contribute proportionally to the mediation of neuroinflammation. Significantly, the peripheral immune system, particularly B- and T-lymphocytes, significantly contribute to generating inflammatory responses within the brain. Typically, peripheral immune cells are scarce in the CNS; however, instances of tissue injury or infection lead to changes in blood-brain barrier (BBB) permeability, allowing peripheral cytokines and chemokines to enter the brain. Despite ongoing investigations, the intricacies of the interaction between the peripheral immune system and neuroinflammation remain incompletely understood, warranting further research efforts to advance appropriate therapeutic strategies for managing PD[25][26].

Observations in PD patients reveal the existence of T cells, encompassing CD3+, CD4+, and CD8+ subtypes, within the SNpc. Interestingly, dopaminergic neurons in this region express MHC-I, which serves as an antigen-presenting molecule and responds to α-synuclein or neuromelanin stimulation, culminating in cytokine secretion[27]. Remarkably, CD8+ T cells actively target and eliminate these neurons, whereas both CD4+ and CD8+ T cells exhibit pivotal roles in generating IL-4 and IFNγ in response to α-synuclein exposure. Additionally, CD4+ T cells have been linked to the early detection of PD motor symptoms. Significantly, the involvement of immune-dependent peptide epitopes hints at possible connections between interaction of mitochondrial and lysosomal mechanisms in PD[28].Under the influence of cytokines and chemokines, several transcription factors, such as NF-κB, AP1, and STAT, undergo upregulation, with NF-κB playing a central role in regulating cytokine production through inflammasomes and immune activation[29].

GSK-3: STRUCTURE, PATHOLOGICAL INVOLVEMENT IN PD

GSK-3, or glycogen synthase kinase 3, is a pivotal regulatory protein involved in various biological processes. Dysfunctions in GSK-3 have links to metabolic disorders like diabetes, cancer, and neurodegenerative diseases. It's a serine-threonine kinase known for phosphorylating downstream targets, including signaling molecules and transcription factors [30]. Acting as a "molecular switch," GSK-3 conveys signals from stimuli like growth factors to influence cell fate. It can be manipulated pharmacologically to enhance functions like survival, proliferation, and neuroplasticity. Structurally, GSK-3 has two lobes: N-terminus and C-terminus. The ATP binding site is near the N-terminus, and the catalytic site is positively charged, near the C-terminus, forming the 'activation loop,. The C-terminus has a crucial tyrosine residue for activation[31].

In the pathogenesis of Parkinson's disease (PD), transcription factors like NF-κB and Snail have substantial roles as inflammatory agents. NF-κB, an inflammatory pathway, is modulated by GSK-3. The NF-κB pathway comprises a complex with IKB, P65, and P50 subunits. Upon stimulation, IKB undergoes phosphorylation by IKB kinase (IKK), leading to its ubiquitination and proteasomal breakdown[32]. This enables active NF-κB to relocate to the nucleus. GSK-3β phosphorylation, prompted by various stressors, LPS, and pathogenic cues, activates NF-κB, causing the transcription of inflammatory mediator genes, an increase in NLRP3 protein levels, and the formation of the inflammasome. Inhibiting GSK-3 can curb NF-κB activity, thereby diminishing inflammation. Snail, a zinc-finger transcription factor, oversees epithelial-mesenchymal transition (EMT) by suppressing E-cadherin, a tumor suppressor, and regulating other epithelial genes. GSK-3β governs Snail protein stability and subcellular positioning through phosphorylation at different motifs. This phosphorylation enables nuclear export, interaction with β-Trcp, and ensuing ubiquitination. GSK-3β can bind and phosphorylate Snail at two phosphodegron motifs, overseeing polyubiquitination and subcellular arrangement. Inhibiting GSK-3 also impacts Snail and E-cadherin expression, increasing and decreasing them, respectively. Hence, Snail and GSK-3 are interlinked through multiple pathways in EMT signaling. Snail-regulated exosomal miR-21 represses NLRP3 inflammasome activity by inhibiting PTEN and BRCC3, causing phosphorylation and ubiquitination of NLRP3 at lysine-63, eventually inhibiting NLRP3 inflammasome assembly in a cancer mouse model. The precise role of Snail protein in PD is yet to be fully comprehended [33][34].

Oxidative stress:
Oxidative imbalance significantly contributes to the degeneration of dopaminergic neurons. Dopamine (DA) degradation through monoamine oxidase (MAO) and tyrosine hydroxylase (TH) generates reactive oxygen species (ROS). MAO produces hydrogen peroxide (H2O2) and hydroxyl (OH) molecules that oxidize cytosolic glutathione (GSH). This oxidation transforms GSH into toxic glutamyl peptides and cysteinyl peptides, causing harm to DA neurons, which results in cell demise. Additionally, this process reduces the activity of mitochondrial complex-1, leading to further ROS production[35].
The interplay between GSK-3β and oxidative stress has been extensively investigated, revealing that oxidative damage downregulates the PI3K/Akt pathway. Under oxidative stress conditions, GSK-3β becomes hyperactive, resulting in the elevation of death signal molecules like Caspase 3 and cytochrome c, while concurrently dampening cell survival cues. Ultimately, this cascade contributes to neuronal cell death. This positioning of GSK-3β as a potential therapeutic target has gained prominence in managing PD. Moreover, the enigmatic presence of GSK-3β within mitochondria has been linked to mitochondrial complex 1 inhibition-induced oxidative damage[36][37].
Oxidative stress-induced NLRP3 activation has long been recognized, with recent insights identifying cathepsin B upregulation as the underlying mechanism. This process fuels neuroinflammation. Rotenone-induced NLRP3 activation leads to pyroptosis, which can be mitigated through NIM811 intervention. Notably, oxidative stress-dependent NLRP3 activation is triggered by Ca+2 influx via TRMP2 receptors, often prompted by liposomes and particulate crystals[38]. Nrf2 activation counteracts oxidative damage-mediated NLRP3 activation. Dimethyl fumarate, an Nrf2 activator, restores balance by addressing oxidative damage, mitochondrial depletion, inflammation, and averting axonal degeneration and locomotor dysfunction in X-linked adrenoleukodystrophy's mouse model. In this context, NLRP3 and GSK-3β are intertwined with oxidative damage through Nrf2-mediated suppression of antioxidant and anti-inflammatory gene transcription [39].

Synucleinopathy:
Synucleinopathy pertains to the pathological mechanism involving α-synuclein aggregation, a major component of Lewy bodies, coded by the SNCA gene. Rotenone induces α-synuclein phosphorylation, escalating aggregation and calcium elevation. In calcium signaling, rotenone impedes Akt-GSK-3β phosphorylation, revealing its role via the calcium/GSK-3β pathway in α-synuclein aggregation[40].α-Synuclein is phosphorylated by GSK-3β, and it can trigger NLRP3 inflammasome assembly through TLR2 stimulation. GSK-3β inhibition curtails α-synuclein levels, safeguarding against PD-associated cellular demise, hinting at neuroprotection for dopaminergic neurons by dampening α-synuclein toxicity [41]. NURR1 transcription is pivotal for dopaminergic neuron differentiation and preservation. Activated α-synuclein triggers GSK-3β activation, causing NURR1 phosphorylation and proteasomal breakdown. GSK-3 inhibition shields against NURR1-linked cell survival decline. Furthermore, α-synuclein directly spurs tau phosphorylation via GSK-3β stimulation. α-Synuclein forms a complex with tau and GSK-3β, and precise regions like the NAC domain and an acidic region promote GSK-3β-mediated tau phosphorylation. Hence, α-synuclein serves as an intermediary linking tau and GSK-3β, culminating in tau phosphorylation by GSK-3β[42][43].
SNCA mutations lead to α-synuclein aggregation in dopaminergic cells, propagating between neurons, exacerbating brain disease progression. α-Synuclein can deactivate the NF-κB pathway, holding a neuroprotective role. In this context, synucleinopathy propels neuroinflammation advancement, as GSK-3β instigates α-synuclein aggregation through phosphorylation, and the amassed α-synuclein stimulates NLRP3 inflammasome formation [44].

Autophagy
The dysregulation of peptide clearance and secretion presents a significant hurdle in the progression of PD. The inadequate removal of proteins through autophagy or ubiquitination pathways to undergo proper clearance is a crucial factor contributing to PD pathology. This can lead to the formation of protein aggregates within neurons, triggering apoptosis, or disrupt of mitochondrial function, which affects the expression of ETC complex[45]. GSK-3β-mediated autophagic inhibition plays a role in NLRP3 inflammasome-mediated inflammatory progression. Inhibition of GSK-3β promotes autophagic activity and NLRP3 activation, while blocking autophagy reverses the suppressive effect on inflammasome activation, indicating that GSK-3β regulates NLRP3 inflammasome activation through autophagy[46]. A compound derived from marine sponges called hymenialdisine exhibits competitive inhibition of ATP, targeting enzymes like GSK-3β, Cdk1, and CK-1, known for hyperphosphorylating tau and MAP proteins. By inhibiting these enzymes, hymenialdisine shows potential therapeutic effects in reducing abnormal phosphorylation associated with PD pathology. Additionally, a small molecule autophagy modulator, 6-Bio,

has demonstrated the ability to enhance autophagy and autolysosome production in dopaminergic neurons, promoting the degradation of SNCA (alpha-synuclein) and clearing toxic protein aggregates in the midbrain region[47].[48]

CONCLUSION

GSK-3β holds a pivotal function in numerous pathological mechanisms, involving autophagic dysregulation, inflammation, oxidative stress, and cellular survival as well as apoptosis. In neurodegenerative and metabolic disorders, the main players in the inflammatory process are GSK-3β and NLRP3. While the molecular link among GSK-3β and other inflammatory proteins such as NLRP3 is not fully understood, it is believed to involve kinases including AMPK and Akt. Recent studies have highlighted the influential interaction among GSK-3β and NLRP3 in the assembly of inflammasomes. Current research suggests that GSK-3β influence NLRP3 mediated inflammation through various mechanisms, including posttranslational alterations of NLRP3, upregulation of transcription factors like NF-κB, or direct induction of microglial stimulation, subsequently leading to NLRP3 inflammasome activation. Besides its well-established associations with inflammatory mediators such as Nrf2, PI3K and Akt, GSK-3β also exhibits emerging interactions with NLRP3 and GLP-1, offering potential therapeutic targets for disease management, albeit with limited documented evidence of their correlation. Developing therapeutic approaches that target multiple pathways simultaneously, the pursuit of disease management advancements lies in investigating strategies such as GSK-3β and NLRP3 inhibition, combining GSK-3β inhibition with Nrf2 induction, or integrating GSK-3β inhibition combined with GLP-1 activation, offering promising therapeutic prospects. Recent studies shows the combination of GSK-3β inhibition and Nrf2 induction with curcumin-diethyl fumarate has shown promising efficacy in PD therapy. In the field of multitarget ligand discovery, there is a need to explore both natural and synthetic compounds to identify pharmacophores or parent rings that can be used to synthesize compounds with desired activities. The current approach of studying the influence of therapeutic agents on individual proteins without considering the interactions with alternative and parallel pathways should be shifted towards a multiple target analysis approach. Simultaneous targeting of multiple proteins not only opens new avenues for drug discovery but also enables the repurposing of existing drugs for suitable diseases based on specific pathological alterations. Therefore, adopting a more comprehensive and multitarget approach in drug discovery research is essential for advancing therapeutic interventions.

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Conflict of Interest

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