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REVIEWS

Therapeutic Potential Effect of Glycogen Synthase Kinase 3 Beta (GSK-3β) Inhibitors in Parkinson Disease: Exploring an Overlooked Avenue

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease of the brain due to degeneration of dopaminergic neurons in the substantia nigra (SN). Glycogen synthase kinase 3 beta (GSK-3β) is implicated in the pathogenesis of PD. Therefore, the purpose of the present review was to revise the mechanistic role of GSK-3β in PD neuropathology, and how GSK-3β inhibitors affect PD neuropathology. GSK-3 is a conserved threonine/serine kinase protein that is intricate in the regulation of cellular anabolic and catabolic pathways by modulating glycogen synthase. Over-expression of GSK-3β is also interconnected with the development of different neurodegenerative diseases. However, the underlying mechanism of GSK-3β in PD neuropathology is not fully clarified. Over-expression of GSK-3β induces the development of PD by triggering mitochondrial dysfunction and oxidative stress in the dopaminergic neurons of the SN. NF-κB and NLRP3 inflammasome are activated in response to dysregulated GSK-3β in PD leading to progressive neuronal injury. Higher expression of GSK-3β in the early stages of PD neuropathology might contribute to the reduction of neuroprotective brain-derived neurotrophic factor (BDNF). Thus, GSK-3β inhibitors may be effective in PD by reducing inflammatory and oxidative stress disorders which are associated with degeneration of dopaminergic in the SN.

Keywords Parkinson's disease · GSK-3β

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease of the brain [1]. PD is characterized by motor symptoms including tremors, rigidity, and bradykinesia, and non-motor such as dementia, cognitive dysfunction, sleep disorders, and depression that may develop by decades before motor symptoms [1, 2]. Aging is the main factor that predisposes the development of PD and is linked with its severity. PD affects 1–3% of the general population aged more than 60 years. However, PD that may be developed below the age of 50 years is known as an early-onset PD, though onset of PD below 21 years is called juvenile PD. PD prevalence is more common in men than women that might due to higher levels of neuroprotective estrogen [3, 4]. The pathogenesis of PD is related to the progressive degeneration of dopaminergic neurons in the substantia nigra (SN) and the accumulation of Lewy bodies in the survival neurons. Lewy bodies are mainly formed by the deposition of α-Syn which is also found in other neurological disorders called synucleinopathies. Of note, loss of 70% of dopaminergic neurons in the SN is developed before the development of PD symptoms [3, 4].

The presence and contribution of α-Syn to PD is controversial and might be pathogenic or a compensatory increased to reduce dopaminergic neuronal loss. Two types of PD are identified, idiopathic (sporadic) PD which form 90% of cases whereas familial PD account for 10% only [5, 6]. Mutation of α-Syn is associated with the development of familial PD [7].

It has been reported that genetic alterations in PD are found since early embryonic life that predispose to the development of PD after the age of 60 years [7]. Genetic alteration can interrelate with different environmental factors in the pathogenesis of PD [8]. It has been hypothesized that

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three temporal phases including triggers (like environmental toxins), facilitators (like peripheral inflammation), and aggravators (like autophagy dysfunction) are required for the pathogenesis of PD [9]. For example, gut dysbiosis and alteration of the nasal microbiome promote the deposition of α-Syn and the development of non-motor symptoms of PD [9]. Systemic inflammation in chronic metabolic disease facilitates neuroinflammation and degeneration of dopaminergic neurons SN with the accumulation of α-Syn [10]. Defective autophagy which acts as an aggravator promotes PD neuropathology by reducing the clearance of α-Syn [9]. Furthermore, mitochondrial dysfunction, oxidative stress, apoptosis, and dysfunction of growth factors contribute to the pathogenesis of PD [11] (Fig. 1).

It has been shown that glycogen synthase kinase 3 beta (GSK-3β) is intricate in the pathogenesis of PD [12]. Though, the underlying mechanism of GSK-3β in PD neuropathology is not fully clarified. Therefore, the objective of the present review was to revise the mechanistic role of GSK-3β in PD neuropathology. In addition, we try to revise the potential therapeutic role of GSK-3β inhibitors in PD.

GSK-3β and Neurodegenerative Disorders

GSK-3 is a conserved threonine/serine kinase protein that regulates cellular anabolic and catabolic pathways by modulating glycogen synthase in response to biological stimuli [13]. In particular, GSK-3 is involved in neurodevelopment and synaptic plasticity, though GSK-3 is implicated in the development of neurodegeneration, cognitive dysfunction and bipolar disorders [14]. Two isozymes of GSK-3 including GSK-3α and GSK-3β are identified; they have 98% similarity with overlapping function [13].

Normally, GSK-3β is expressed in all brain regions; however, GSK-3α is expressed in specific brain regions such as the cerebral cortex, hippocampus, and Purkinje cells [15]. Signaling pathways involved with GSK-3β are mainly

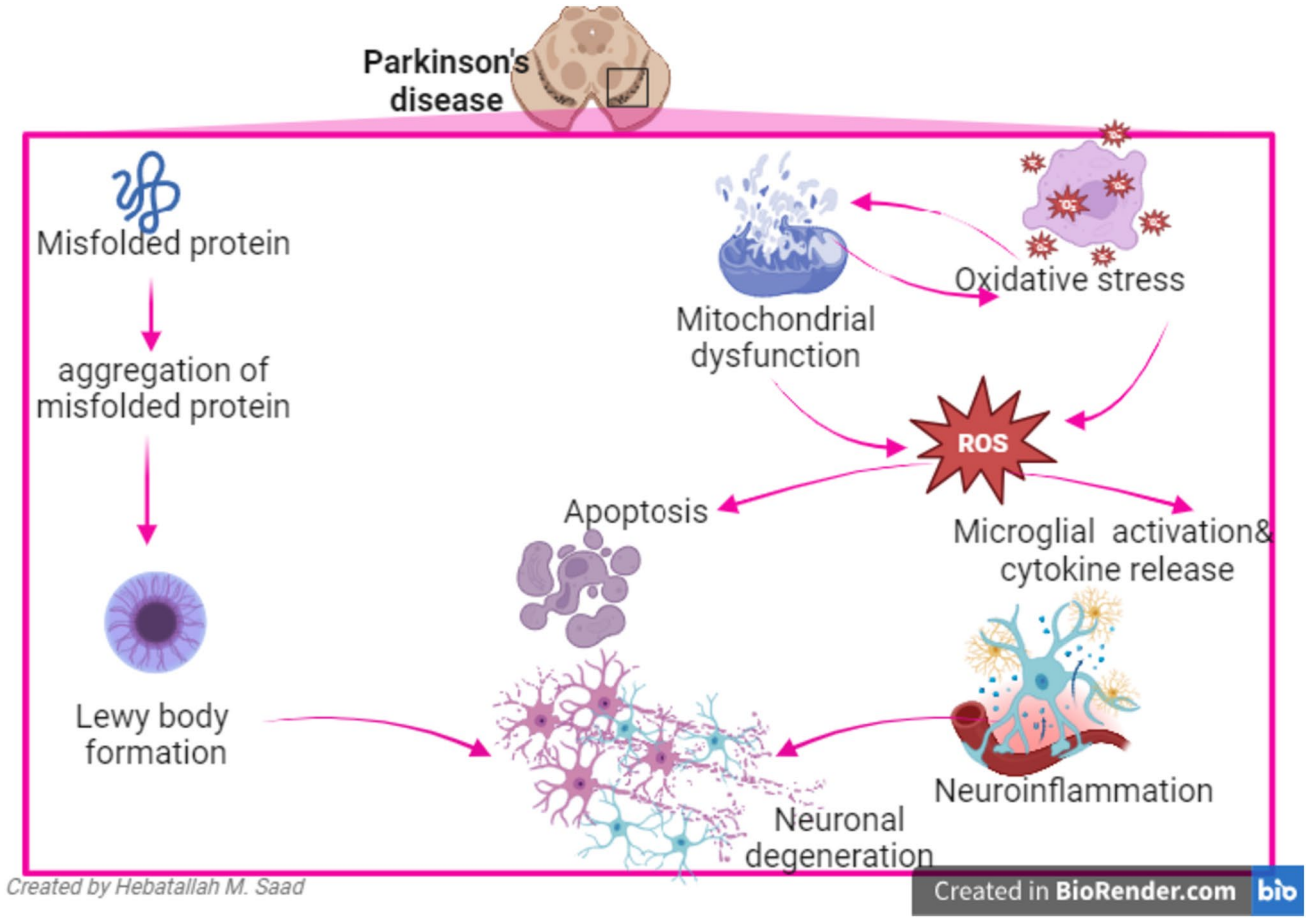

Fig. 1 Pathophysiology of PD: induction formation of misfolded proteins by different causes promote aggregation of misfolded proteins and formation of Lewy body which induce neuronal degeneration. In addition, development of mitochondrial dysfunction and oxidative by different causative factors implicated in the pathogenesis lead to generation of reactive oxygen species (ROS) which cause direct neuronal apoptosis or indirectly through activation of microglia and the development of neuroinflammation lead to neuronal degeneration

phosphoinositol 3 phosphatase kinase (PI3K) and Wnt/β-catenin [16]. GSK-3β regulates cell cycle signaling, cell proliferation, and DNA repair [17]. In addition, GSK-3β regulates cellular oxidative stress through modulation of the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) [18]. Findings from preclinical and clinical studies illustrated that exaggerated GSK-3β activity is involved in progressive neurodegeneration in different neurodegenerative diseases [19–21].

Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by progressive memory loss and cognitive impairment [22]. AD is developed due to progressive deposition of extracellular amyloid beta (Aβ) protein and intracellular neurofibrillary tangles (NFTs) which are formed by hyperphosphorylation of tau protein [23]. Accumulated Aβ in AD induces upregulation of GSK-3β which increases the activation of amyloid precursor protein (APP) leading to the generation of Aβ in a vicious cycle. Therefore, GSK-3β activity is augmented in AD leading to synaptic failure and impairment of synaptic plasticity leading to cognitive decline [19]. Moreover, GSK-3β promotes tau protein phosphorylation-induced neurodegeneration and increases AD neuropathology.

However, the underlying mechanism for the overactivation of GSK-3β is remaining unidentified [19, 24]. Normally, GSK-3β activity is negatively inhibited by phosphorylation on ser9-like protein kinase A (PKA) by insulin and insulin and insulin-like growth factor 1 (IGF-1). Dysregulation of this pathway as in insulin resistance (IR) induces overexpression of GSK-3β [19, 25]. Brain IR in diabetes is associated with activation of GSK-3β due to failure of insulin and IGF-1 signaling [25]. A cohort study that involved AD patients showed that the active form of GSK-3β was increased in the frontal cortex neurons in the early stages of AD patients before accumulation of NFTs [24]. GSK-3β activation is energetic by phosphorylation of tau protein which results in disturbance of neuronal synaptic activity and the formation of neuronal plaques. Though the accumulation of Aβ plaques and intracellular NFTs has been well recognized as neuropathological hallmarks of the disease, the molecular mechanism has not been elucidated [24]. It has been shown that ginsenoside improves cognitive function by regulating oxidative stress, apoptosis, and neuroinflammation in experimental AD by inhibiting GSK-3β [26]. Likewise, tolfenamic acid constrains GSK-3β-mediated tau hyperphosphorylation in AD models [27]. This finding suggests that GSK-3β could be a primary event in the development of AD (Fig. 2). Therefore, inhibition of exaggerated GSK-3β could be effective against AD neuropathology.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons, motor cortex, and corticospinal tract linked with GSK-3β overactivity [28]. GSK3β activity shows an increase in various ALS models and patients. Furthermore, GSK3β inhibition can suppress the defective phenotypes in various ALS models [29]. GSK3β expression and cytosolic levels of GSK3β are augmented in the spinal cord and frontotemporal cortex of ALS patients [21]. Preclinical findings support that GSK-3β activity is increased in ALS animals and patients [29]. In addition, the expression of GSK-3β and catenin which reflect the activity of GSK-3β had been reported to be increased in the frontal cortex and hippocampus in ALS patients [30]. Activation of GSK-3β in ALS is related to the downregulation of PI3K, and PI3K activators may be effective in the management of ALS [31]. To identify the therapeutic potential of GSK3β-targeted drugs in ALS treatment, many studies have shown that GSK3β inhibitors can attenuate ALS disease progression. Valproic acid which is a mood stabilizer can indirectly inhibit GSK3β via Akt pathway. Valproic acid acts as a neuroprotective for motor neurons, delays disease progression, and extends life span in mouse ALS model [21]. A combination of lithium and valproic acid showed superior effects on motor dysfunction and disease progression in mouse ALS model by inhibiting GSK3β compared to lithium and valproic acid when used alone [32]. Therefore, GSK3β activity is increased in numerous ALS and GSK3β inhibition can rescue defective phenotypes of ALS in numerous models.

Multiple Sclerosis

Multiple sclerosis (MS) is the most common demyelinating neurodegenerative disease of the central nervous system (CNS) in young adults [32, 33]. MS is regarded as an autoimmune disease causing injury of myelin sheath by immune cells and inhibiting the production of myelin. Oligodendrocytes which involved with the synthesis of the myelin sheath are typically affected in MS [33, 34]. In demyelinating diseases as in MS and experimental autoimmune encephalomyelitis (EAE) , GSK-3β activity is increased [20, 35]. It has been shown that the expression of GSK-3β is highly increased in MS patients mainly in the cerebral cortex and corpus callosum [15]. Higher expression of GSK-3β is increased in MS and induces the development of neuroinflammation by activating the release of pro-inflammatory cytokines via TLR4-dependent pathway [36, 37]. It has been established that GSK3β is intricate in Wnt-beta-catenin signaling, which participates to the inhibition of myelination and remyelination processes in humans [38]. dGSK3β rs334558 polymorphism is a susceptibility factor for MS, as it is found in the promoter region, a possible explanatory mechanism that could be an influence of

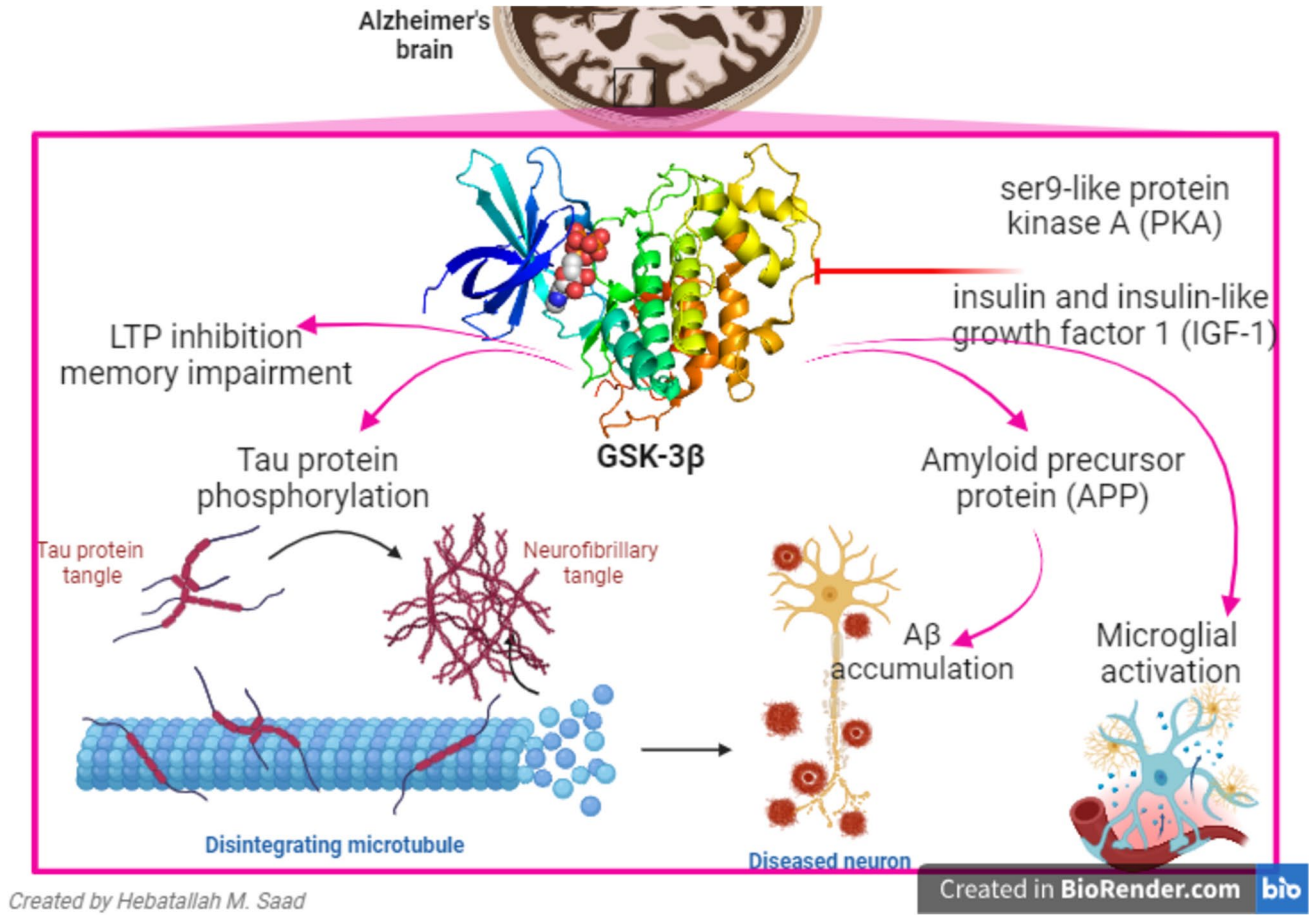

Fig. 2 Role of GSK-3β in Alzheimer disease (AD): GSK-3β has an important role in the pathogenesis of AD by inducing amyloid precursor protein (APP) processing for Aβ and activation of microglia. GSK-3β by increasing tau protein phosphorylation causes memory impairment and inhibition of long-term potentiation (LTP). GSK-3β is inhibited by ser9-like protein kinase A (PKA) and insulin-like growth factor 1 (IGF-1)

the variant on the gene transcription rate [39]. Lithium treatment significantly delayed the onset of EAE and improves its severity by inhibiting pro-inflammatory TNF-α and inactivated GSK-3β [20]. Furthermore, lithium improves stem cell differentiation into oligodendrocytes and enhances re-myelination in MS [38]. Thus, exaggeration of GSK-3β is linked with MS neuropathology, and GSK-3β inhibitors may be effective in the management of MS.

Taken together, over-expression of GSK-3β is linked with the development of different neurodegenerative diseases, and GSK-3β inhibitors could be a novel therapeutic strategy in the management of neurodegenerative diseases.

The Possible Role of GSK-3β in PD

It has been observed that GSK-3β over-activity is correlated with PD neuropathology by inducing neuroinflammation, derangement of blood-brain barrier (BBB) permeability, and degeneration of dopaminergic neurons in the SN [12]. A previous preclinical study found that 6-hydroxydopamine (6-OHDA)-induced dopaminergic degeneration is mediated by the expression of GSK-3β [40]. In 6-OHDA-induced PD, the activated GSK-3β not only induces degeneration of dopaminergic neurons but also blocks the proliferation and differentiation of neuron stem cells, thereby blocking neurogenesis [41]. Many studies have exposed that the inhibition of GSK-3β reduces dopaminergic neuron injury induced by MPTP toxicity, indicating the association of GSK-3β with the pathogenesis of PD [42]. Khan et al. [43] showed that GSK-3β accelerates neuroinflammation in PD by triggering the expression of pro-inflammatory cytokines. The harmful effect of GSK-3β activation on dopaminergic neuron survival was further established in transgenic mice expressing a constitutively active mutant of GSK-3β [40]. Dysregulation of GSK-3β results in aberrant mitochondrial function, which is implicated in PD [43]. Considerable evidence suggests that GSK-3β mediates glial cell activation and promotes the

release of pro-inflammatory cytokines via regulating several transcriptional factors and development of neuroinflammation [44]. Moreover, GSK-3β is increased in the striatum of postmortem brains of PD patients [45]. GSK-3β was activated by phosphorylation at its Tyr216 in the striatum of PD patients [36]. Increased GSK-3β protein levels have also been reported in peripheral blood lymphocytes in PD patients [46]. Therefore, GSK-3β overactivity promotes PD neuropathology through induction of mitochondrial dysfunction and neuroinflammation.

Furthermore, GSK-3β may contribute to the formation of protein aggregates or intracellular inclusions in PD. Deficiency of autophagy-lysosomal pathway, leading to dysfunction of protein aggregate clearance, was observed in postmortem brains of PD patients [47]. GSK-3β may progressively lead to intracellular and axonal deposit in PD neuropathology [43, 47]. GSK-3β inhibits autophagy leading to reduction in the clearance of α-Syn .GSK-3β is known to be involved in neuronal development and suppression of GSK-3β showed the ability to reduce α-Syn in cellular models of PD [48]. It has been observed that exaggerated GSK-3β inhibits dopaminergic neurotransmission in the SN [12]. The dopamine D2 receptor regulates Akt and may also target the Wnt pathway, two signaling cascades that inhibit GSK-3β [12, 48]. In addition, abnormal dopaminergic activity is associated with PD due to overactivity of GSK-3*β*. Inhibition of GSK-3*β* has been reported to attenuate D1 receptor agonist-induced hyperactivity in mice [49]. Synaptic loss is correlated with cognitive deficits in PD. Synaptic dysfunction leads to impairment of the balance between long-term potentiation (LTP) and long-term depression (LTD). Of note, LTP inhibits GSK-3β activity which required for LTD. Though the precise mechanism underlying this remains indistinct, it has been established that constitutive GSK-3β activity promotes basal AMPAR endocytosis leading to inhibition of synaptic plasticity and development of cognitive dysfunction in PD [43, 50]. Thus, exaggerated GSK-3*β* can induce structural and functional alterations in the dopaminergic neurons of SN in PD.

As well, α-Syn activates the expression and forms a heterotrimeric complex with GSK-3β. The activation of GSK-3β was absolutely dependent on the presence of α-Syn, as indexed by the absence of p-GSK-3β in cells lacking α-Syn and in α-Syn knockout mice. In turn, GSK-3β promotes aggregation of α-Syn [51]. Autopsies from postmortem PD brains revealed that levels of phosphorylated GSK-3β were higher in PD patients as compared to healthy controls [52]. Evidence from preclinical and clinical studies revealed that GSK-3β expression is augmented in PD [53]. Of interest, GSK-3β polymorphism increases PD risk [54]. In a mouse model of tauopathy, GSK-3β expression is co-localized with α-Syn in the striatum [55]. Remarkably, a neuroprotective protein progranulin which is highly reduced in PD modulates the expression of GSK-3β [56, 57]. Mutation of progranulin is associated with over-expression of GSK-3β and the development of PD [57].

The activation of Nrf2 enhances the expression of ARE and hemeoxygenase-1 (HO-1), which decreases excessive cellular stress, mitochondrial dysfunction, apoptosis, and neuronal degeneration, which is the major cause of motor dysfunction including PD [58]. Therefore, there is a link between GSK-3β and the Nrf2/HO-1 signaling pathway in PD [58]. Over-expression of the GSK-3β and downregulation of the Nrf2/ARE pathway are responsible for a decrease in anti-oxidant defense effects. These underline the usefulness of dual GSK-3β inhibitors/Nrf2 inducers. Thus, a dual modulator, the structures of a curcumin-based analogue, as GSK-3β inhibitor, and a diethyl fumarate fragment, as Nrf2 inducer, could be effective in PD [59]. These preclinical and clinical findings proposed that over-expression of GSK-3β are linked with the pathogenesis of PD. Though, the mechanisms by which GSK-3β promotes PD neuropathology are not well elucidated.

Mechanistic Role of GSK-3β in PD

Mitochondrial Dysfunction and Oxidative Stress

Reactive oxygen species (ROS) are produced continuously by all body tissues that are eliminated by endogenous anti-oxidant capacity [60–62]. When there is an imbalance between ROS generation and anti-oxidant capacity, oxidative stress is developed [63]. The mitochondria are the major site for the generation of ROS which affect mitochondrial DNA leading to more ROS generation. It has been reported that oxidative stress plays a critical role in the degeneration of dopaminergic neurons in the SN [64]. Of note, dopamine turnover and environmental neurotoxins induce mitochondrial dysfunction which promotes the development and progression of oxidative stress [65]. Dopamine outside the synaptic vesicle undergoes auto-oxidation or is metabolized by monoamine oxidase (MAO) to form ROS which induces mitochondrial dysfunction [66]. Interestingly, mitochondrial dysfunction is highly related to augments ROS generation in PD [67]. Importantly, complex I deficiency of the respiratory chain is associated with the pathogenesis of PD [64]. In the experimental PD model, rotenone or MPTP can induce inhibition of mitochondrial complex I and reduce ATP formation with subsequent injury and degeneration of dopaminergic neurons in the SN [68]. In clinical settings, oxidative stress biomarkers were reported to be increased in PD patients compared to healthy controls [69]. Overall, these findings indicated that mitochondrial dysfunction and oxidative stress are closely related to PD neuropathology.

On the other hand, GSK-3β is intricate in the pathogenesis of PD through modulation of mitochondrial dysfunction and oxidative stress [70]. In vitro study demonstrated that oxidative stress promotes the expression of GSK-3β which inhibits transcription of anti-oxidant Nrf2 leading to propagation of oxidative stress-induced neuronal injury [70]. Liu et al. [71] observed that inhibition of GSK-3β attenuates oxidative stress-induced kidney injury in rats by upregulation of the Nrf2 signaling pathway. Likewise, insulin and IGF-1 inhibit oxidative stress in rat cortical neurons by reducing the expression of GSK-3β [72]. In vivo and in vitro studies confirmed that inhibition of GSK-3β attenuates the development and progression of mitochondrial dysfunction and oxidative stress in mice with muscle dysfunction [73]. These verdicts proposed that GSK-3β over-activity induces the development of PD by triggering mitochondrial dysfunction and oxidative stress in the dopaminergic neurons of the SN (Fig. 3).

Inflammatory Signaling Pathways

It has been reported that different inflammatory signaling such as nuclear factor kappa B (NF-κB) and nod-like receptor pyrin 3 (NLRP3) inflammasome are intricate in the pathogenesis of PD [4]. NF-κB is an inflammatory signaling protein that promotes the expression and release of chemokines and pro-inflammatory cytokines. NF-κB is involved in the regulation of cell differentiation, proliferation, apoptosis, and innate and adaptive immune response [74]. It has been reported that NF-κB can induce degeneration of dopaminergic neurons in the SN [75]. Aging-induced immune dysregulation promotes NF-κB expression and associated degeneration of dopaminergic neurons in the SN [75].

Notoriously, released α-Syn from injured neurons triggers NF-κB activation and expression of pro-inflammatory cytokines. In injured neuron triggers NF-κB activation, and induces further degeneration of dopaminergic neurons in the

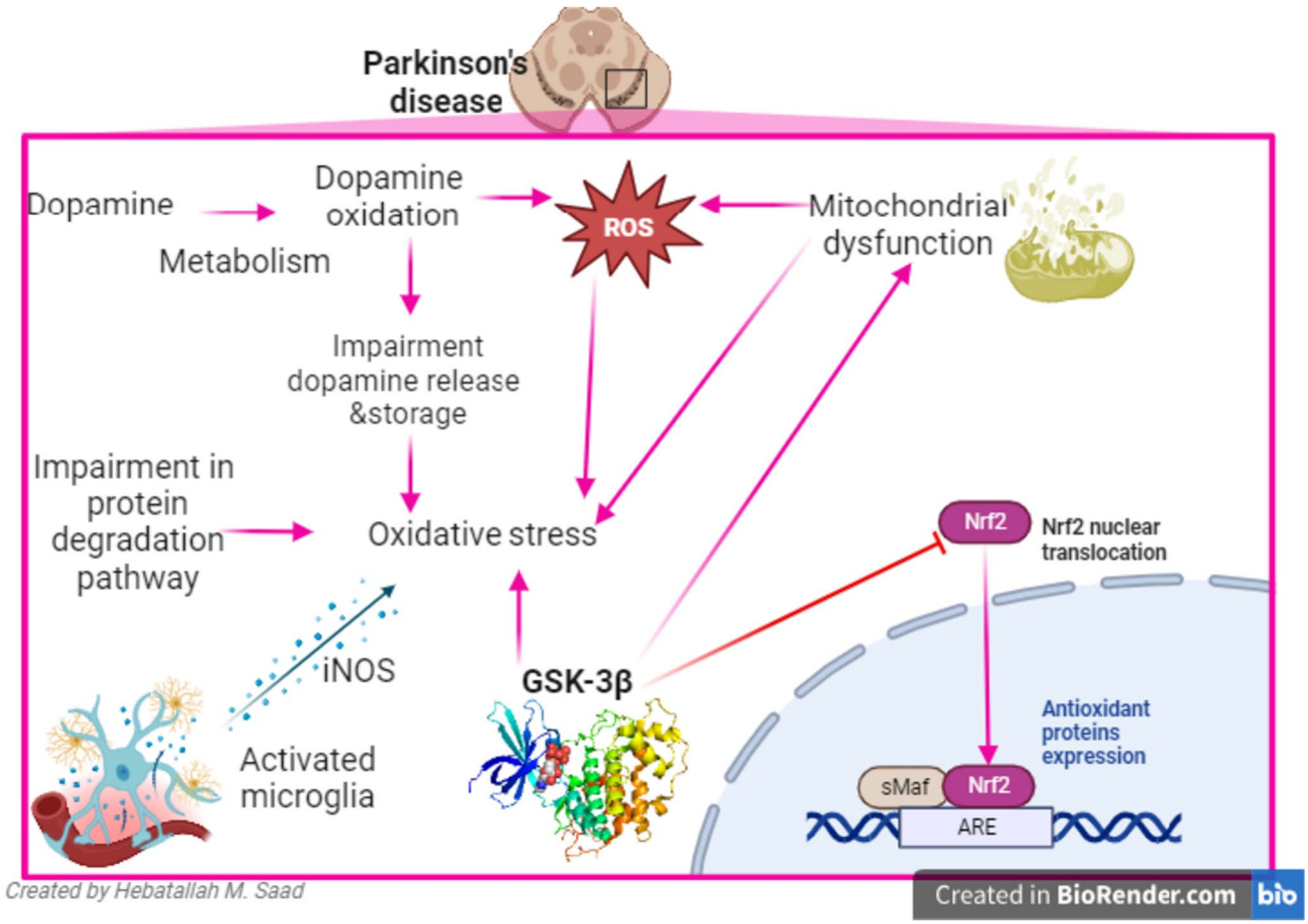

Fig. 3 Role of GSK-3β in PD: oxidative stress is a central mechanism intricate in the pathogenesis of PD. Dopamine metabolism and mitochondrial dysfunction induce formation of reactive oxygen species (ROS) which causes oxidative stress. Beside, impairment of protein degradation pathway promotes oxidative stress. Activated microglia and GSK-3β accelerate oxidative stress by inhibiting the expression of anti-oxidant proteins such as nuclear factor-related erythroid factor (Nrf2) with inhibition of anti-oxidant response element (ARE)

SN [75]. Besides, exaggerated GSK-3β signaling activates the expression of NF-κB as confirmed in an in vitro study [76]. In an experimental study, inhibition of GSK-3β by selective inhibitors decrease NF-κB activation in rats [77].

Furthermore, NLRP3 inflammasome is a multiprotein complex involved in the release of IL-1β and IL-18 via caspase activation [78]. NLRP3 inflammasome is activated by various stimuli in conical and non-conical pathways. NLRP3 inflammasome is regarded as a metabolic sensor detects inflammatory and oxidative stress injury [78]. Different studies revealed that activated NLRP3 inflammasome signaling pathway triggers the release of pro-inflammatory cytokines, development of neuroinflammation, and degeneration of dopaminergic neurons in the SN [79, 80]. Furthermore, NLRP3 inflammasome-induced pyroptosis could be the potential mechanism for the development of PD. Indeed, NLRP3 inflammasome interacts with α-Syn leading to progressive neuronal degeneration. Therefore, NLRP3 inflammasome level is correlated with α-Syn level in PD patients [81]. It has been shown that GSK-3β triggers the expression of NLRP3 inflammasome leading to pyroptosis [82]. Besides, GSK-3β via inhibition of the Nrf2 signaling pathway promotes oxidative stress which enhances activation of NLRP3 inflammasome [83].

Therefore, NF-κB and NLRP3 inflammasome are activated in response to over-activated GSK-3β in PD leading to progressive neuronal injury (Fig. 4).

Neuroinflammation

Neuroinflammation is an immune response of the CNS to exogenous infectious agents or endogenous stress stimuli as in many neurological disorders such as neurodegenerative diseases [84]. Microglia and astrocytes are intricate in the development of neuroinflammation; nevertheless, peripheral immune cells which traverse injured BBB can involve the development of neuroinflammation in chronic inflammatory disorders [85]. Neuroinflammation in the

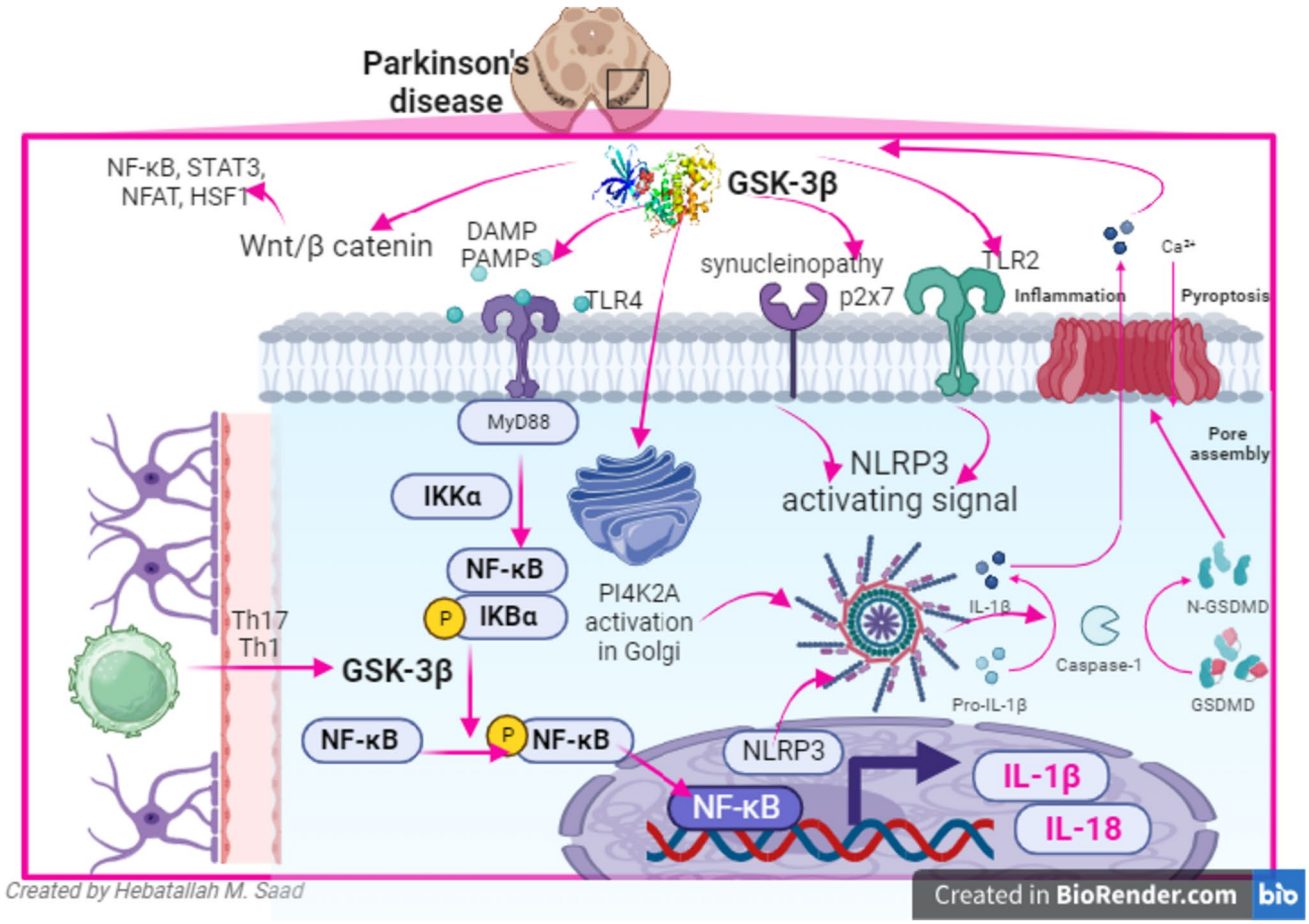

Fig. 4 Inflammatory signaling pathways and GSK-3β in PD: GSK-3β triggers the interaction between pathogen-associated molecular pattern molecules (PAMP) and damage-associated molecular pattern (DAMP) with toll-like receptor 4 (TLR4) which promote NF-κB which induce the expression of NLRP3 inflammasome leading to the release of pro-inflammatory cytokines. GSK-3β via activation of TLR2 and p2×7 also induce the expression of NLRP3 inflammasome

acute phase is defended to eradicate the underlying cause; however, chronic neuroinflammation may induce neuronal injury, synaptic dysfunction, and exacerbation of brain neuropathology [86]. Different genetic and epidemiological studies confirmed the potential role of neuroinflammation in PD neuropathology [48]. Postmortem study revealed that microglia and T cells are highly concentrated in the SN of PD brains due to dysregulation of innate and adaptive immune responses [87]. Evidence from preclinical studies showed that neuroinflammation is correlated with progressive degeneration of dopaminergic neurons in the SN [88]. Findings from postmortem analysis illustrated that levels of pro-inflammatory cytokines in the CSF were increased in PD patients compared to healthy controls [88]. Pro-inflammatory cytokines activate inflammatory signaling pathways leading to oxidative stress injury of dopaminergic neurons in the SN [88]. Remarkably, Th1 and Th17 enhance MPTP-mediated injury of dopaminergic neurons in the SN [89]. As well, neuroinflammatory biomarkers are increased in PD patients compared to healthy controls [90]. Besides, many studies highlighted that GSK-3β promotes the progression of neuroinflammation by inducing the expression of inflammatory signaling pathways and pro-inflammatory cytokines [43, 91]. Furthermore, different preclinical studies confirmed that inhibition of GSK-3β leads to attenuation of neuroinflammation in different neurodegenerative disorders including PD [92, 93]. For example, Lee et al. [94] revealed that inhibition of GSK-3β by specific peptide attenuates nigrostriatal neurodegeneration in rat PD models. These findings proposed that GSK-3β plays a crucial role in the development and progression of neuroinflammation in PD.

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin protein family concerned in the resistance toward neuronal injury [95]. BDNF acts on tyrosine kinase receptor B (TrkB) and p75NT receptor (p75NTR) [92]. BDNF is released from specific brain regions including the hypothalamus, hippocampus, and limbic system [96–98]. It has been shown that BDNF serum level is reduced in PD patients compared to healthy controls [99]. However, in advanced stages of PD neuropathology BDNF serum level is increased as a compensatory mechanism to mitigate oxidative and inflammatory disorders [99]. Chang et al. [100] confirmed that activation of BDNF signaling reduces motor deficit and cognitive dysfunction in the mouse PD model. Improvement of BDNF signaling by anti-depressants promotes cognitive and motor functions in PD patients [101].

In relation to GSK-3β, BDNF inhibits GSK-3β activity by increasing PI3K in neural stem cells [102]. Likewise, BDNF attenuates phencyclidine-induced apoptosis via activation of PI3K and inhibition of GSK-3β in cultured cortico-striatal neurons [103]. Of note, GSK-3β-induced neuropsychiatric disorders are mediated by inhibition of BDNF signaling [104]. These findings proposed a reciprocal relationship between BDNF and GSK-3β. Therefore, higher expression of GSK-3β in the early stages of PD neuropathology might contribute in the reduction of BDNF leading to progressive neuronal injury.

GSK-3β Inhibitors in PD

GSK-3β is a central point in a number of signaling pathways in the pathogenesis of this neurodegenerative disease, affecting multiple pathological events involved in dopaminergic neuron degeneration, thus providing a potential target in the therapeutic management by blocking the pathogenic pathways involved in PD pathogenesis. GSK-3 inhibition has been considered a potential therapeutic strategy for PD treatment [12]. In the last decades the scientific community has been working to understand the role of GSK-3 with the aim in mind of design efficient and selectivity GSK-3 inhibitors. However, so far clinical and preclinical GSK-3 inhibitors have been both sub-optimal regarding potency, poor GSK-3β selectivity over other CNS targets and closely related kinases, low CNS exposure, and chronic toxicity. Research into GSK-3β inhibitors relay primarily on identification of the new use of the known GSK-3β inhibitors and the development of them in order to improve selectivity and toxicity. Many efforts have been done for using of GSK-3β inhibitors in the management of neurodegenerative diseases including PD [105]. GSK-3β inhibitors are categorized into 4 classes according to Ruiz et al. [106]: (I) cationic GSK-3β inhibitors including lithium, copper, and zinc; (II) ATP blockers which inhibit ATP binding kinase such as synthetic organic molecules; (III) allosteric inhibitors; and (IV) substrate competitive inhibitors. However, synthetic GSK-3β inhibitors are non-specific that may inhibit other kinases. In addition, drug resistance is higher among GSK-3β inhibitors due to the mutation of ATP binding sites of GSK-3β [107]. Most of the clinical trials for the use and safety of GSK-3β inhibitors were conflicting and did not reach Phase III [108]. Since GSK-3β has a critical role in metabolism, insulin signaling, protein regulation, and inflammation, GSK-3β inhibition is regarded as an attractive target for therapeutic intervention in metabolic and neurodegenerative diseases [105]. Though, the design of specific inhibitors of intracellular kinases including GSK-3β is very difficult because the kinase families share conserved ATP-binding sites, and consequently, currently developed kinase inhibitors have mostly off-target effects [109]. Since GSK-3β is a constitutively active kinase, extreme GSK-3β inhibition could have adverse effects by

disrupting its physiological roles. For example, SB216763, a well-known GSK-3β inhibitor, was effective in attenuating Aβ-induced neurotoxicity in an AD model, but it induced neuronal death, gliosis, and behavioral deficits in control animals [110]. Thus, it would be important to design a GSK-3β inhibitor to selectively inhibit the activity of the kinase when it is excessively activated in a pathological condition without affecting its physiological roles in normal condition.

Additional significant challenge to overcome for a GSK-3β inhibitors to be converted in an effective drug for PD treatment is its specific brain distribution. The drug needs to cross the BBB to exert its action in the regulation of exacerbated GSK-3β brain levels. Usually this is not an easy task for GSK-3β inhibitors when oral bioavailability is the preferred administration route for chronic PD treatment. It is very difficult to balance the equilibrium between molecular lipophilicity to enter into the brain and molecular hydrophilicity to be orally administrated. That reason has ruled out several promising GSK-3β inhibitors into the market. Determination of potential brain penetration should be incorporated in the first stages of GSK-3β inhibitor development. Therefore, GSK-3β inhibitors which cannot cross BBB have limited efficacy in the management of neurodegenerative diseases [111]. Despite these findings, different GSK-3β inhibitors reached the market for the treatment of different diseases.

Interestingly, clinical side effects of GSK-3β inhibitors are rather scarce since a limited number of GSK-3β inhibitors have reached the clinical phase [112]. GSK-3β may lead to hyperglycemia by inhibiting the conversion of glucose to glycogen via inhibition of glycogen synthase [113]. This function is modulated by insulin which activates glycogen synthase and inhibits GSK-3β activity by about 50% [72]. Furthermore, GSK-3β inhibitors are of distinct chemical structures and thus differ in their bio-clinical and pharmacological properties. Thus, it is difficult to decide at this point what adverse events will be commonly associated with inhibition of GSK-3β inhibitors [112]. Lithium is the only GSK-3β inhibitor that has been in clinical use for a significant time. Though, lithium lacks target specificity, and its adverse side effects and high toxicity do not necessarily reflect events linked with inhibition of GSK-3β [114]. AZD-1080 and NP-12/Tideglusib (Noscria) reached the clinic in 2006. AZD-1080 was withdrawn due to nephrotoxicity observed in phase I clinical trials [115]. NP-12 in phase IIb trials for AD and paralysis supranuclear palsy and no side effects/off targets effects have been described at this time [116]. Their discrete chemical structures and/or different inhibition mode are most likely responsible for the different clinical impacts observed with these two compounds [115, 116]. Results from TAURUS and ARGO studies will disclose the safety and efficacy of tideglusib in humans [117]. In the meantime, an increasing number of GSK-3β inhibitors are being tested in preclinical models, and it is anticipated that some will enter clinical trials [118].

Of note, concerns had been raised regarding the potential toxicity of GSK-3β inhibitors ranging from hypoglycemia to tumorigenesis and neuron deregulation [119]. GSK-3β is vital for life, and there is a disquiet that its inhibition could prevent cells from functioning normally. However, GSK-3β activity is elevated in pathological conditions; thus, a smooth inhibition of GSK-3 able to restore down levels of activity to physiological ones would be enough to produce an important therapeutic effects in diseases, being that point crucial for not producing adverse effects. Therefore, GSK-3β inhibitors increase insulin sensitivity and may increase cell proliferation via Wnt signaling-dependent pathway [119]. In addition, the interaction of Wnt/β-catenin due to GSK-3β inhibition promotes oncogene transcription and increases the risk of malignancy [120]. Activation of the proto-oncogenic molecule β-catenin by inhibition of GSK-3 is another major concern claiming that long-term inhibition of GSK-3β may promote cancer. However, no direct in vivo evidence has indicated tumorigenesis upon administration of GSK-3β inhibitors. On the contrary, in certain cancers GSK-3β inhibitors reduced cell proliferation and enhanced cell death upon irradiation treatment [120].

However, GSK-3β inhibitor lithium which was used for a long time in the management of bipolar disorders was not associated with hypoglycemia and malignancies [121]. Lithium inhibits 25% of GSK-3β without effect on Wnt/β-catenin signaling which increases cell proliferation [121].

Therefore, repurposing of other drugs with well-known pharmacokinetic/pharmacodynamic profiles that have inhibitory effects on GSK-3β seems to be more appropriate in the management of PD.

Lithium

Lithium is a chemical element present as pegmatic mineral. Lithium salts are widely used in the management of various neurological disorders including mania, bipolar disorders, AD, and schizophrenia [122]. It was approved by FDA in 1970 for use in the management of bipolar disorders. Lithium was first used in the nineteenth century for the treatment of gout [123]. In 1949, lithium was re-introduced in treating mania and other bipolar disorders [123]. The main mechanism of action of lithium is related to increasing serotonin synthesis and inhibits the synthesis of norepinephrine [124]. The fundamental mechanism of lithium is through inhibition of inositol monophosphatase which is required for conversion of inositol monophosphate to inositol which is implicated in the pathogenesis of bipolar disorders [124]. As well, lithium blocks GSK-3β directly or indirectly via inhibition of the mechanistic target of rapamycin (mTOR) which is a necessary downstream signaling of GSK-3β [121]. In mania,

GSK-3β activity is augmented by the over-activity of dopamine signaling, leading to inhibition of both cAMP-response element binding protein (CREB) and β-catenin. Furthermore, lithium inhibits both NO signaling and NMDA receptors [125]. Different preclinical studies revealed that lithium can inhibit GSK-3β and prevents the accumulation of tau protein in AD mouse model [126]. As well, lithium attenuates MPTP-induced dopaminergic neuronal injury in PD mouse model [127]. The underlying neuroprotective effect of lithium, in PD, is related to the inhibition of GSK-3β and oxidative and activation of neuroprotective BDNF [127]. In virtue of its anti-oxidant and neuroprotective effects, lithium seems to be effective in PD. However, due to its relative toxicity and wide-spectrum adverse effects, a large dose of lithium is not appropriate monotherapy in the management of PD. Thus, low non-toxic dose of lithium in combination with other anti-PD agents seems more effective. Of note, only one ongoing trial using lithium in PD illustrated that medium-dose lithium improves disease progression measured by brain MRI, but it is poorly tolerated by 33% of PD patients [128]. Further PD clinical research is merited examining lithium's tolerability; effects on biomarkers and potential disease-modifying effects are recommended.

Famotidine

Famotidine is an H2 blocker used in the management of peptic ulcers and gastroesophageal reflux disease. It was patented in 1979 and become available in the market in 1985. Famotidine is a rapid-acting drug with minimal adverse effects, though a large therapeutic dose of it may cause seizures [129, 130]. It has been shown that famotidine has a neuroprotective effect by inhibiting GSK-3β expression in MK-801-induced toxicity in SH-SY5Y cell line [131]. In addition, famotidine attenuates ketamine-induced schizophrenic behavior in rats by inhibiting GSK-3β [132]. A previous pilot study on 7 PD patients revealed that daily intake of 80 mg/day of famotidine for 6 weeks improve motor [133]. Of interest, famotidine enhances the therapeutic efficacy of levodopa and improves non-motor symptoms in PD patients [134]. However, famotidine has no clinical benefit against the development of levodopa-induced dyskinesia [135].

Naproxen

Naproxen is an analgesic and anti-inflammatory drug belonging to the non-steroidal anti-inflammatory drug (NSAID). It acts by reversible inhibition of cyclooxygenase enzymes (COXs), i.e., non-selective COX inhibitors [136]. It has been reported by preclinical investigations that naproxen has anti-diabetic effects by inhibiting GSK-3β activity [137]. Furthermore, naproxen attenuates carcinogenesis by inhibiting GSK-3β and modulation of Wnt/β-catenin signaling [137]. As well, naproxen has an anti-cancer effect via inhibition of GSK-3β [138]. In general, NSAIDs have neuroprotective effects against PD neuropathology by inhibiting neuroinflammation and abnormal immune response. In addition, non-selective COX inhibitor ibuprofen also has a chemo-preventive efficacy against cancer by inhibiting GSK-3β and modulating Wnt/β-catenin signaling [139]. Notably, ibuprofen was reported to be effective in the management of PD [140]. Therefore, NSAIDs with inhibitory effects on GSK-3β could be effective in the management of PD.

Metformin

Metformin is an insulin-sensitizing drug used as first-line therapy in the management of type 2 diabetes (T2D) [141]. Metformin has pleiotropic effects through modulation of inflammation and oxidative stress [141]. A recent study conducted by Alrouji et al. [142] suggested that metformin has a double-sword effect against PD neuropathology. The neuroprotective effect of metformin against PD is through inhibition of inflammation and oxidative stress. However, its detrimental effect is related to the development of B12 deficiency and hyperhomocysteinemia [142]. Nevertheless, prolonged use of metformin seems to be protective rather than harmful [143]. On the other hand, metformin has a cytoprotective effect by inhibiting the expression and activity of GSK-3β in non-small-cell lung cancer [144]. Similarly, metformin attenuates mitochondrial dysfunction and associated oxidative stress by inhibiting GSK-3β in preosteoblast [145]. Metformin acts by activating AMPK [146] and AMPK activators have been observed to protect dopaminergic neurons in the SN [147]. It has been shown that AMPK activator GSK621 attenuates MPTP mouse PD model. AMPK activator GSK621 dramatically ameliorated PD by increasing the levels of dopamine and rescuing the loss of dopaminergic neurons, which is dependent on the mitochondrial pathway. Regulation of AMPK/GSK-3β/PP2A pathway-related proteins by GSK621 was partially inhibited the development of PD, suggesting that a negative feedback loop exists between AMPK action and mitochondrial dysfunction-mediated apoptosis. Therefore, mitochondrial dysfunction and apoptosis in the pathogenesis of PD might be mediated by AMPK/GSK-3β/PP2A pathway action, which might be a promising new option for future therapy of PD [147]. Moreover, flavonoid dihydromyricetin has a potent anti-oxidative agent against MPTP-induced behavioral impairment in mice by inhibiting GSK-3β through AMPK-dependent pathway [148].

Therefore, the neuroprotective effect of metformin against PD may be mediated by inhibiting GSK-3β.

Tideglusib

Tideglusib is a small molecule that inhibits GSK-3β irreversibly. It is regarded as a non-ATP competitive inhibitor of GSK-3β used in different neurodegenerative diseases [107]. Tideglusib has a neuroprotective effect against MPTP-induced dopaminergic injury in mice in a dose-dependent manner via inhibition of GSK-3β [46]. Likewise, tideglusib attenuates 6-OHDA and lipopolysaccharide (LPS) PD animal model by inhibiting GSK-3β in the dopaminergic neurons of the SN [149]. Furthermore, tideglusib reduces oxidative stress in the dopaminergic neurons of the SN by inducing the expression of anti-oxidant enzymes [150]. In addition, tideglusib can decrease the risk of progressive dopaminergic neurodegeneration induced by neuroinflammation which is augmented in response to GSK-3β [151]. Therefore, tideglusib seems to be effective in PD. In addition, tideglusib has also shown acceptable safety and was well tolerated in several chronic clinical trials regarding different neurological diseases [152–157]. However, tideglusib failed in a Phase II clinical trial of AD due to no clinical benefits in cognitive improvement despite its neuroprotection in preclinical AD models [155]. Therefore, intervention at an earlier disease stage, longer duration of treatment, and better dosing of tideglusib should be taken into account for future clinical trials that should also be considered in clinical trials for PD, which may possibly be confronted with similar problems.

Taken together, GSK-3β inhibitors could be effective in PD by reducing inflammatory and oxidative stress disorders which are associated with degeneration of dopaminergic neurodegeneration.

Future Research and Perspective

Most of the recently developed GSK-3β inhibitors fall into the ATP competitive inhibitors which are characterized by good safety and low specificity but tend to induce drug resistance. Although their discovery is more challenging, compounds that recognize other regions of the kinase are considered a favorable choice as the target is more conserved. Therefore, GSK-3β inhibitors mainly lithium and tideglusib could be effective as adjuvant treatments in the management of PD by reducing neuroinflammation and degeneration of dopaminergic neurons in the SN [106]. A combination of lithium plus L-DOPA could be a substantial combination in the management of PD. It has been reported that lithium in combination with L-DOPA play not only as a neuroprotectant, but also for reducing abnormal involuntary movements and possibly alleviating potential side effects associated with the current treatment for PD [158]. However, chronic lithium use is associated with an increased incidence of dopaminergic drug use compared with anti-depressants, identifying a prescribing cascade related to lithium use in the elderly. Whether this reflects inappropriate treatment of action tremor or treatment of drug-induced Parkinsonism should be evaluated by a close examination of prescribing practices [159]. Moreover, lithium has hypoglycemic effect and improves the function of pancreatic β cells through inhibition of GSK-3β [160]. Likewise, anti-diabetic metformin which has an inhibitory effect on GSK-3β [147] may reduce PD neuropathology. Thus, GSK-3β inhibitors could be more effective in PD with associated comorbidities such T2D and psychiatric disorders.

Therefore, selective use of GSK-3β inhibitors with good efficacy and high safety in combination with anti-PD medications might be a novel therapeutic strategy in the management of PD.

Conclusions

PD is a progressive neurodegenerative disease of the brain may be linked with over-activation of GSK-3β which is a conserved threonine/serine kinase protein involved in the regulation of cellular anabolic and catabolic pathways. Overexpression of GSK-3β is also linked with the development of neurodegenerative diseases such as AD, ALS, and MS. NF-κB and NLRP3 inflammasome are activated in response to dysregulated GSK-3β in PD leading to progressive neuronal injury. Higher expression of GSK-3β in the early stages of PD neuropathology might contribute to the reduction of neuroprotective BDNF. Thus, GSK-3β inhibitors could be effective in PD by reducing inflammatory and oxidative stress disorders which are associated with dopaminergic neurodegeneration. Furthermore, preclinical and large-scale prospective studies are warranted in this regard.

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Declarations

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