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*Review Article*

# GSK-3 in Neurodegenerative Diseases

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Glycogen synthase kinase-3 (GSK-3) regulates multiple cellular processes, and its dysregulation is implicated in the pathogenesis of diverse diseases. In this paper we will focus on the dysfunction of GSK-3 in Alzheimer's disease and Parkinson's disease. Specifically, GSK-3 is known to interact with tau, $\beta$-amyloid (A$\beta$), and $\alpha$-synuclein, and as such may be crucially involved in both diseases. A$\beta$ production, for example, is regulated by GSK-3, and its toxicity is mediated by GSK-induced tau phosphorylation and degeneration. $\alpha$-synuclein is a substrate for GSK-3 and GSK-3 inhibition protects against Parkinsonian toxins. Lithium, a GSK-3 inhibitor, has also been shown to affect tau, A$\beta$, and $\alpha$-synuclein in cell culture, and transgenic animal models. Thus, understanding the role of GSK-3 in neurodegenerative diseases will enhance our understanding of the basic mechanisms underlying the pathogenesis of these disorders and also facilitate the identification of new therapeutic avenues.

## 1. Introduction: GSK-3 Isoforms, Expression, and Neuronal Regulation

Glycogen synthase kinase-3 (GSK-3) is a cellular serine/threonine protein kinase [1, 2], belonging to the glycogen synthase kinase family [1]. It is involved in a number of cellular processes, including the division, proliferation, differentiation, and adhesion of cells [3]. Dysfunction of GSK-3 is implicated in diverse human diseases, including Alzheimer's disease (AD), Parkinson's Disease (PD), type 2 diabetes, bipolar disorder (BPD), and cancer [3, 4]. Two isoforms of GSK-3 have been identified, namely, GSK-3$\alpha$ and GSK-3$\beta$, which although encoded by different genes are similarly regulated [5]. GSK-3$\alpha$ (51 kDa) differs to GSK-3$\beta$ (47 kDa) in that the former has a glycine-rich extension at the amino-terminal end of the protein [5]. Both isoforms are ubiquitously expressed throughout the brain, with high levels of expression seen in the hippocampus, cerebral cortex, and the Purkinje cells of the cerebellum [6]. The expression ratio of these isoforms, however, favors GSK-3$\beta$ [6, 7].

The crystal structure of GSK-3$\beta$ reveals a catalytically active dimer [8] conformation that progressively phosphorylates substrates with Ser/Thr pentad repeats [9]. Despite having disparate sequences, the isoforms have a conserved functional domain and share similar substrates, while remaining pharmacologically distinguishable [3]. The independent deletion of GSK-3 isoforms in mice resulted in a distinct profile of substrate phosphorylation [10], suggesting different functions of GSK-3 isoforms in the brain.

The activity of GSK-3 is dependent on phosphorylation at specific sites; phosphorylation of Ser9 of GSK-3$\beta$, or Ser21 of GSK-3$\alpha$, inhibits activity [9], whereas phosphorylation of Tyr216 on GSK-3$\beta$ and Tyr279 on GSK-3$\alpha$ increases activity [3]. It is thought that deactivation of GSK-3 has more influence on activity rather than activation, as the enzyme is constitutively active and the activation sites can undergo autophosphorylation [11].

The most well-studied GSK-3 regulation pathway is through Akt activation. Insulin stimulation, for example, can activate phosphatidylinositol 3-kinase (PI3K), which phosphorylates Akt (protein kinase B) and in turn inhibits GSK-3 [12–15]. A brief exposure to insulin, however, can also transiently activate GSK-3$\beta$ by phosphorylating Tyr216 through Fyn, a nonreceptor tyrosine kinase [13]. Other kinases, such as protein kinase C (PKC), inhibit GSK-3 activity by phosphorylating Ser9 [14, 16, 17]. The inhibition

by PKC is additive to the inhibition by PI3K [14]. Additionally, within the brain, p38 mitogen-activated protein kinase (MAPK) inactivates GSK-3$\beta$ by direct phosphorylation at its C-terminus [18].

Dephosphorylation of GSK-3 at inhibitory sites (thus activating the protein), is coordinated by protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A), and protein phosphatase 2B (PP2B, calcineurin) [19–21]. PP1 preferentially acts as a phosphatase for GSK-3$\beta$, while PP2A favors GSK-3$\alpha$ [19]. On the other hand, the overexpression of GSK-3$\beta$ inhibits PP2A, which may serve as a negative feedback mechanism for GSK-3$\beta$ activity [22]. GSK-3 and its complex regulatory mechanisms have been extensively studied in a number of neurodegenerative diseases as outlined below.

## 2. GSK-3 in AD and Tauopathies

Alzheimer's disease is characterized by the accumulation of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) within the brain (for a review, see [23]). The major component of the plaques, which was first purified and identified from AD brains in the 1980s [24] and later shown to be a product of normal cellular metabolism [25], is $\beta$-amyloid (A$\beta$). A$\beta$ is proteolytically processed from the amyloid precursor protein (APP) [26] via cleavage at the $\beta$-secretase site by BACE1 [27], followed by $\gamma$-secretase cleavage by presenilin (PS) [28]. The key component of the NFTs on the other hand, is the tau protein [29–31], which was originally identified as an intracellular microtubule stabilizer [32]. Both A$\beta$ and tau are, therefore, fundamentally involved in driving the pathogenesis of AD. With respect to this paper then, it is of note that both these proteins may be modulated by GSK-3. The most well-characterised interactions, however, occur with tau.

*2.1. Tau.* GSK-3 is one of the main kinases involved in the phosphorylation of tau, a process that is crucial to the function of the protein. The normal phosphorylation of tau determines its affinity for microtubule binding [29, 33–35], with pathological hyperphosphorylation resulting in the dissociation of tau from microtubules and subsequent aggregation to form NFTs (for a review, see [36]). GSK-3$\beta$ has been found to be associated with normal microtubule-bound tau [37] as well as with the hyperphosphorylated tau deposits in the AD brain [38, 39]. There are several lines of evidence that support a direct functional link between tau phosphorylation and GSK-3. For example, *in vitro* and in cell culture models, both GSK-3$\alpha$ and GSK-3$\beta$ can phosphorylate tau at various sites that are consistent with the epitopes found to be hyperphosphorylated in AD brains [40–45]. The overexpression of GSK-3$\beta$ in animal models also promotes the phosphorylation of tau, implicating it as an *in vivo* tau kinase [46–49]. Conversely, the inhibition of GSK-3$\beta$ activity by either GSK-3 inhibitors or upstream Akt inhibitors reduces tau phosphorylation [50–58]. GSK-3$\beta$ thus affects tau function through interfering with tau phosphorylation, thereby disrupting microtubule stability [59, 60], self-assembly of microtubules [61, 62], the microtubule-dependent cell processes [63], and regulation of organelle transport and axonal transportation [64–66]. Interestingly, the overexpression of tau also increased GSK-3$\beta$ activity, which perpetuated the phosphorylation of tau [67].

In addition to effects on phosphorylation, the activation of GSK-3$\beta$ may also facilitate the aggregation of tau [68–71]. Furthermore, the *in vivo* overexpression of GSK-3$\beta$ accelerates tau-induced neurodegeneration [47, 49, 71, 72], while the inhibition of its activity reduces tau toxicity [73–75]. Conversely, in the absence of tau, the neurodegenerative and cognitive phenotype observed in GSK3-overexpresing mice is ameliorated, suggesting that tau may mediate GSK-3$\beta$ toxicity [76]. In addition, GSK-3 may regulate tau-mRNA splicing [77] and expression [78] by disrupting transcription [79].

*2.2. β-Amyloid.* Accumulating evidence suggests that GSK-3 interferes with the biology of A$\beta$, which is believed to be upstream of tau in the pathogenesis of AD [23]. A$\beta$ accelerates tau pathology [80, 81] and promotes tau phosphorylation by several mechanisms, including activation of GSK-3$\beta$ [82–84]. The use of A$\beta$ antibodies both *in vitro* and *in vivo* decreases GSK-3 activity, supporting the interaction between A$\beta$ and GSK-3 [85]. It has also been shown that the activation of GSK by A$\beta$ in primary hippocampal cultures is specific to GSK-3$\beta$ [86], and that the inhibition of GSK-3$\beta$ prevents A$\beta$-induced toxicity to neurons [82, 84, 87, 88]. Likewise, although both isoforms of GSK-3 are hyperactivated in transgenic mice expressing mutant APP (V717I) [89], the data from this model together with that from a model expressing the intracellular domain of APP [90] firmly support the notion that it is the activation of GSK-3$\beta$ by amyloid that results in downstream pathological effects on tau. The A$\beta$-induced activation of GSK-3 also only needs to be transient to result in tau hyperphosphorylation and other effects such as mitochondrial trafficking impairments [91]. Finally, tau null mice are protected against A$\beta$-induced toxicity [92, 93] and GSK-induced toxicity [76], which taken together with the discussed data highlight the complex interaction between GSK, A$\beta$, and tau. This is further complicated by the fact that GSK-3 is involved in APP processing and subsequent A$\beta$ production.

The amyloid precursor protein and PS1 are substrates of GSK-3 [94–98], and GSK-3$\alpha$ is thought to regulate A$\beta$ production by interfering with APP cleavage at the $\gamma$-secretase step [99]. Co-overexpression of GSK-3$\alpha$ and APP in CHO cells increased the level of A$\beta$ in a dose-dependent manner, while selective reduction of GSK-3$\alpha$ protein expression by RNAi decreased A$\beta$ levels [99]. Although Phiel et al. [99] showed an opposite role of GSK-3$\beta$ in their study, GSK-3$\beta$ was later shown to decrease A$\beta$ levels by an unknown pathway [100]. Nevertheless, the genetic or pharmacological deactivation of GSK-3 reduces A$\beta$ and its associated toxicity, ameliorates A$\beta$-induced behavioral deficits, and rescues neuronal loss in APP-overexpressing mouse models [101–103], thus strongly implicating GSK-3 in the pathogenesis of AD.

## 3. GSK-3 in Parkinson's Disease

Parkinson's disease is characterized by dopaminergic neuron degeneration in the substantia nigra pars compacta (SNpc) with Lewy body (LB) pathology, accompanied by clinically defined parkinsonism [104]. As there is a potential role of tau emerging in PD [105–107], then the function of GSK-3 in PD has also thus been investigated. The examination of postmortem tissue from PD patients has revealed that GSK-3$\beta$, phosphorylated at Ser9, is specifically localised within the halo of LBs [108] and that GSK-3$\beta$ activity is also elevated in the striatum [109]. This latter finding has been recapitulated in mouse models of PD [110]. Increased GSK-3 levels have also been reported in peripheral blood lymphocytes in PD patients [111], and polymorphisms in GSK-3$\beta$, which affect its transcription and splicing, are also associated with disease risk in PD when stratifying by tau haplotype [112, 113].

Mechanistically there is evidence to support an interaction between $\alpha$-synuclein, a 16 kDa natively unstructured protein that is fundamentally involved in the pathogenesis of PD, and GSK. Aggregated $\alpha$-synuclein species are the main component of LBs and single nucleotide polymorphisms and duplication or triplication of the $\alpha$-synuclein gene cause familial Parkinsonian degeneration [104]. $\alpha$-synuclein, which is a substrate for GSK-3$\beta$ phosphorylation, may also modulate the activation of GSK-3$\beta$ [114]; GSK-3$\beta$ phosphorylation at Tyr216 (which activates GSK-3 activity) is also abolished in cells lacking $\alpha$-synuclein and in $\alpha$-synuclein knockout mice [110]. The potential role of GSK-3$\beta$ in PD has been elucidated in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD, where the inhibition of GSK-3$\beta$ protects against MPTP toxicity *in vitro* and *in vivo* [56, 110, 115] and decreases $\alpha$-synuclein protein expression [56]. Taken together, these data strongly implicate GSK-3 in the pathogenesis of PD. The neuroprotective possibilities of GSK-3 inhibition on A$\beta$, tau and $\alpha$-synuclein pathology have thus been explored in depth, most extensively with lithium.

## 4. Lithium: A GSK-3 Inhibitor

Lithium, a monovalent cation, affects multiple cellular processes in model organisms and humans (for a review, see [116]). Importantly, it has been used as a mood stabilizer and primary therapy for BPD since its discovery by Cade in 1949 [117]. Although effective in many cases, lithium exhibits a narrow therapeutic window, and side effects may occur within the therapeutic dose range [118]. Lithium is suggested to have several molecular targets in BPD, one leading mechanism of action is the inhibition of GSK-3 [116].

Haplo-insufficiency of GSK-3$\beta$ mimics behavioral and molecular effects of lithium [119], while GSK-3$\beta$ overexpression mimics mania and hyperactivity in a mouse model [120], supporting GSK-3$\beta$ as a relevant target of lithium action [121]. With an inhibitory Ki of 2 mM [121], lithium inhibits both GSK-3$\alpha$ and GSK-3$\beta$ directly through competitive inhibition of $Mg^{2+}$ [122], and indirectly through the modulation of post-translational modifications of GSK-3 [123, 124] in a number of species [125]. Lithium is selective for GSK-3$\alpha$ and GSK-3$\beta$ and does not inhibit other protein kinases tested *in vitro* and *in vivo*, including casein kinase II, protein kinase A and C, MAPK, and CDK5 [121, 126]. When utilized at therapeutic concentrations in various cell culture models, lithium reduces tau phosphorylation [53, 127–129] and the processing of APP to generate A$\beta$ [99, 130, 131], suggesting that lithium may have important implications in both AD and BPD. However, some of these findings have been disputed, with lithium shown to increase $\beta$-secretase activity and to subsequently elevate extracellular A$\beta$ levels in CHO cells and rat cortical neurons [132]. In this case, the activity of $\gamma$-secretase was unaltered, suggesting that the lithium-induced elevation of A$\beta$ was independent of GSK-3 inhibition [132]. In addition, lithium treatment has been shown to reduce tau protein and mRNA levels in cultured cortical neurons [79].

Nevertheless, lithium has been assessed for its potential efficacy in treating "AD-like" pathology *in vivo*. In wild-type rats, lithium has been shown to reduce tau phosphorylation and inhibit GSK-3 activity [133] and to also enhance spatial memory [134, 135]. Using transgenic animals characterised by progressive A$\beta$ deposition, lithium treatment has been consistently found to decrease A$\beta$ levels and APP phosphorylation, as well as to reduce GSK-3 activity and tau phosphorylation [99, 101, 136–138]. In contrast to previous cell culture studies, however, $\beta$-secretase activity has been unaffected [101, 132]. Lithium treatment has also been shown to prevent A$\beta$ toxicity [136], preserve dendritic structure [101], facilitate neurogenesis [138], and rescue A$\beta$-induced cognitive impairment [101, 137, 138].

Less clear, however, is the efficacy of lithium against tau-mediated degeneration. Mice that overexpress disease-linked tau exhibit reduced tau phosphorylation with lithium treatment [55, 73–75, 139]. In addition, tau transgenic models have attenuated axonal degeneration with lithium treatment [55], but no motor or working memory recovery [139]. Lithium-treated 3XTg mice (harbouring both tau and A$\beta$ pathology) have reduced GSK-3 activity and tau phosphorylation, but no change in A$\beta$ levels or working memory [126]. However, in accordance with cell culture studies [53, 127–129] GSK-3 activity remained the same in a long-term (5 months) lithium trial [74], possibly suggesting that the protection offered by lithium is GSK-3 independent. The authors [74] alternatively suggested that lithium reduced the tau lesion primarily by promoting its ubiquitination and degradation rather than by inhibiting its phosphorylation through GSK-3.

While these *in vitro* and *in vivo* studies reveal a beneficial effect of lithium on tau and A$\beta$ pathology, a number of observational studies and case reports have provided conflicting evidence, with both positive [140–144] and negative outcomes [145, 146] on dementia reported. Despite this, lithium has recently been evaluated as a therapy for AD in a 10-week multicenter, randomized, single-blind, and placebo-controlled trial [147]. GSK-3 activity was monitored in lymphocytes at 1-2 week intervals, total and phosphorylated tau levels were assessed in the CSF, and $A\beta_{(1-42)}$ levels were assessed in the CSF and plasma at the end of

treatment. Cognitive function was assessed using the Mini-Mental State Examination (MMSE), the Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Neuropsychiatric Inventory (NPI). The study concluded that lithium was not an effective therapeutic for AD, as there were no significant effects on any of the endpoint measurements. A post-hoc examination on a subset of individuals did, however, reveal an increase in serum BDNF that was inversely correlated with decreased ADAS-Cog sum scores [148]. Further long-term studies are required to determine the safety and efficiency of lithium or other GSK-3 inhibitors for the treatment of AD.

In pursuit of GSK-3 regulation in PD, lithium has also been tested in animal models of this disease. The data, however, are not conclusive, with lithium shown to both protect against the dopamine depletion resulting from MPTP toxicity [149] and to also cause a decrease in brain dopamine (DA) release [150] that leads to deficits in DA levels [151]. Furthermore, lithium treatment does not prevent dopaminergic neuron loss in the related 6-OHDA model of PD [152]. There is, therefore, currently little evidence to support lithium as a treatment strategy for PD. The data on the use of lithium in other human neurodegenerative diseases is also not compelling.

Lithium, for example, has also been investigated as a therapy for one of the motor-neuron diseases, amyotrophic lateral sclerosis (ALS), despite the lack of an established connection with GSK-3. Although lithium was found to delay disease onset and to reduce neurological deficits in both ALS mouse models and a small human trial [153, 154], other mouse and human trials have shown detrimental effects [155, 156]. The potential utility of lithium in ALS, or indeed in any of the neurodegenerative disorders outlined above, remains unclear. It is likely that lithium has other activities, independent of GSK-3, that may mediate its pharmacodynamics.

## 5. Concluding Remarks

We have summarized the latest knowledge regarding GSK-3 and its involvement in neurodegenerative diseases such as AD and PD. Although extensive research has been undertaken in the last decade, the role of GSK-3 in disease pathogenesis has yet to be fully elucidated. The inhibition of GSK-3 may be a potential target for AD, since it has regulatory effects on both A$\beta$ and tau. Similarly, GSK-3 inhibition could interact with $\alpha$-synuclein to affect the pathogenesis of PD. The intriguing preclinical data, however, has yet to be translated into an effective pharmacotherapy for neurodegeneration, perhaps in part owing to the complex regulation of GSK and its activity on multiple substrates. Future endeavors should investigate alternative modulators of GSK-3 and annotate more precise mechanisms of how the isoforms of GSK-3 participate in neurodegeneration.

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