

Review Article

GSK3 Function in the Brain during Development, Neuronal Plasticity, and Neurodegeneration

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GSK3 has diverse functions, including an important role in brain pathology. In this paper, we address the primary functions of GSK3 in development and neuroplasticity, which appear to be interrelated and to mediate age-associated neurological diseases. Specifically, GSK3 plays a pivotal role in controlling neuronal progenitor proliferation and establishment of neuronal polarity during development, and the upstream and downstream signals modulating neuronal GSK3 function affect cytoskeletal reorganization and neuroplasticity throughout the lifespan. Modulation of GSK3 in brain areas subserving cognitive function has become a major focus for treating neuropsychiatric and neurodegenerative diseases. As a crucial node that mediates a variety of neuronal processes, GSK3 is proposed to be a therapeutic target for restoration of synaptic functioning and cognition, particularly in Alzheimer's disease.

1. GSK3 Signaling Pathway

Many diseases of the central nervous system are characterized by changes in the structural organization of neuronal networks, developmental abnormalities, or dysregulation of signaling pathways, leading to altered brain plasticity and, ultimately, neurodegeneration. The proline-directed serine/threonine kinase, glycogen synthase kinase 3 (GSK3), has been suspected to be a contributing factor in psychiatric illness and age-associated neurodegenerative diseases for some time [1]. The involvement of GSK3 misregulation in a variety of brain abnormalities strongly supports its pivotal role as a metabolic crossroads for controlling basic mechanisms of neuronal function from brain bioenergetics to establishment of neuronal circuits, modulation of neuronal polarity, migration, neuronal proliferation, and survival [2]. In particular, the role of GSK3 in phosphorylation of cytoskeletal proteins impacts neuronal plasticity, as cytoskeletal constituents are involved in the development and maintenance of neurites, and changes in the rate of stabilization/destabilization of microtubules (MT) could

influence major cellular compartments of neurons, such as dendrites, spines, axons, and synapses.

The metabolic function of GSK3 was first described in glycogen metabolism, as GSK3 phosphorylates glycogen synthase in response to insulin [3]. Since then, research has identified a multitude of substrates and functions for this enzyme. GSK3 exists in cells as two distinct gene products, α and β , which exhibit high homology in the catalytic domain but differ in the N- and C-terminal sequences [4]. GSK3 is ubiquitous throughout the animal kingdom [5] and is widely expressed in all tissues with particularly abundant levels in the brain [4], where the neuron-specific isoform GSK3 β 2 is found [6].

GSK3 is unique because it is constitutively active, and upstream signals downregulate its activity by phosphorylation at specific residues. The most important phosphoresidues are serine (Ser) 21 for GSK3 α and Ser9 for GSK3 β , which inhibit its kinase activity [2, 7–10], while phosphorylation on tyrosine (Tyr) residues (Tyr 216/279 for GSK3 β and GSK3 α , resp.), is required for its activation [11–13]. The latter kind of phosphorylation is mediated by

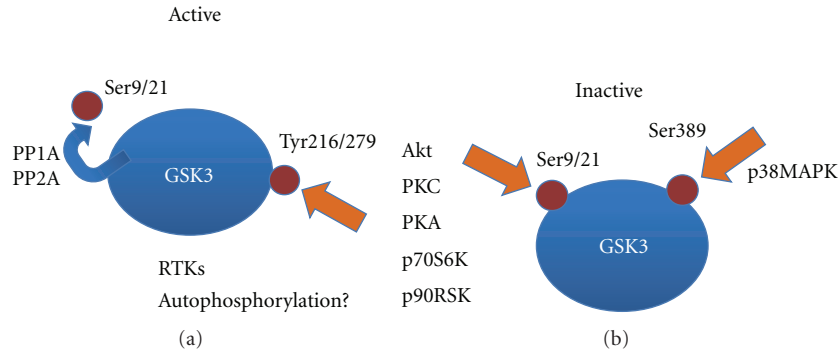


FIGURE 1: Modulation of GSK3 activity by phosphorylation. Protein phosphatases 1 and 2A activate GSK3 by removing Ser9/21 phosphorylation. It has also been reported that phosphorylation in tyrosine residues by members of the receptor tyrosine kinase family of cell surface receptors (RTKs) or by autophosphorylation may activate GSK3. On the other hand, signaling networks activate several protein kinases, which may bring about phosphorylation of different residues and inhibition of GSK3.

diverse tyrosine kinases [14] or by autophosphorylation [15] (Figure 1).

Multiple kinases can phosphorylate Ser21/9, including Akt, protein kinases A and C, p70S6K, and p90RSK [16]. In contrast, protein phosphatases 1 (PP1) and 2A (PP2A) dephosphorylate the inhibitory site of GSK3, resulting in activation of the enzyme. In addition to the inhibitory phosphorylation of GSK3 β described above, an additional inhibitory site at Ser389 has been detected in the brain, which is phosphorylated by p38 mitogen-activated protein kinase (MAPK) [17].

In addition to its phosphorylation state, GSK3 activity may be regulated by proteolysis through disruption of the axin- β -catenin complex [18] or N-terminal cleavage by the calcium-dependent protease calpain [19]. GSK3 activity also depends on its cellular localization. Although GSK3 is predominantly located in the cytosol, it is also present in nuclei and mitochondria, where it is highly activated compared with the cytosolic pool [20]. Nuclear GSK3 regulates the expression of diverse genes via various transcription factors, such as Ap-1, β -catenin, c-myc, and p53 [16]. Subtle control of GSK3-mediated activation and inhibition is required to ensure a proper balance among cell morphoregulation, proliferation, and growth. Thus, prolonged inhibition of GSK3 is associated with hypertrophic cell growth [21], while sustained activation is associated with neurodegeneration [22]. Unlike other kinases, the majority of GSK3 substrates require a “priming” phosphorylation on Ser/Thr residues, which is catalyzed by a protein kinase other than GSK3 [2, 10, 16].

2. Implications of GSK3 Activity in Brain

In adulthood, both GSK3 α and GSK3 β are expressed in mice adult brain and are particularly enriched in hippocampus, neocortex, and cerebellum [23]. In rodent adult hippocampus GSK3 β is more abundant than GSK3 α [24], and in aged hippocampus GSK3 β is elevated, but not GSK3 α [25]. Two splice variants of the GSK3 β gene are found in neurons from mouse, rat, and human: GSK3 β 1 and GSK3 β 2, the

latter being highly expressed during brain development and specific to neurons [6, 26–28]. The two isoforms are differentially involved in phosphorylation of different substrates [29] and establishment of neuronal polarity and axon guidance [2, 30–32].

The importance of GSK3 in brain function has been established by several studies in transgenic mice, which have shown different neurological defects depending of the specific GSK3 isoform involved. While deletion of GSK3 β is lethal, heterozygote mice survive and present increased anxiety and reduced exploration [33–35]. Conversely, knockout GSK3 α mice are quite normal [36], although neuron-specific knockout of GSK3 α results in reduced anxiety, locomotor activity, and aggression [37]. Overexpression of an inhibitory phosphorylation-resistant form of GSK3 results in increased locomotor activity and has been proposed as a model of manic illness [38]. Moreover, overexpressed GSK3 β in dentate gyrus results in tau-dependent neurodegeneration of this region [39]. In the brain, GSK3 regulates developmental processes, including neurogenesis, migration, axon growth and guidance, and synaptic plasticity [40], and its activity is controlled through several signaling pathways activated by growth factors, wingless (Wnt) proteins, G-protein-coupled receptors (GPCR), β -arrestin, among other proteins [41].

Abnormal activation of GSK3 has been associated with several neurological and psychiatric disorders that share developmental abnormalities and altered neurocircuitry maintenance, such as schizophrenia, bipolar disorder, autism, and Alzheimer's disease (AD) [42–46]. GSK3 is indeed a common therapeutic target for neuropsychiatric drugs [41, 47].

3. Signaling Pathways Involved in GSK3 Activity in Brain

GSK3 is a downstream component of several signaling pathways in the brain. One of the most studied is the phosphoinositide-3-OH kinase (PI3K)/Akt pathway, which plays a crucial role in differentiation and survival of neuronal and glial cells [48]. Growth signals, Ras proteins [49],

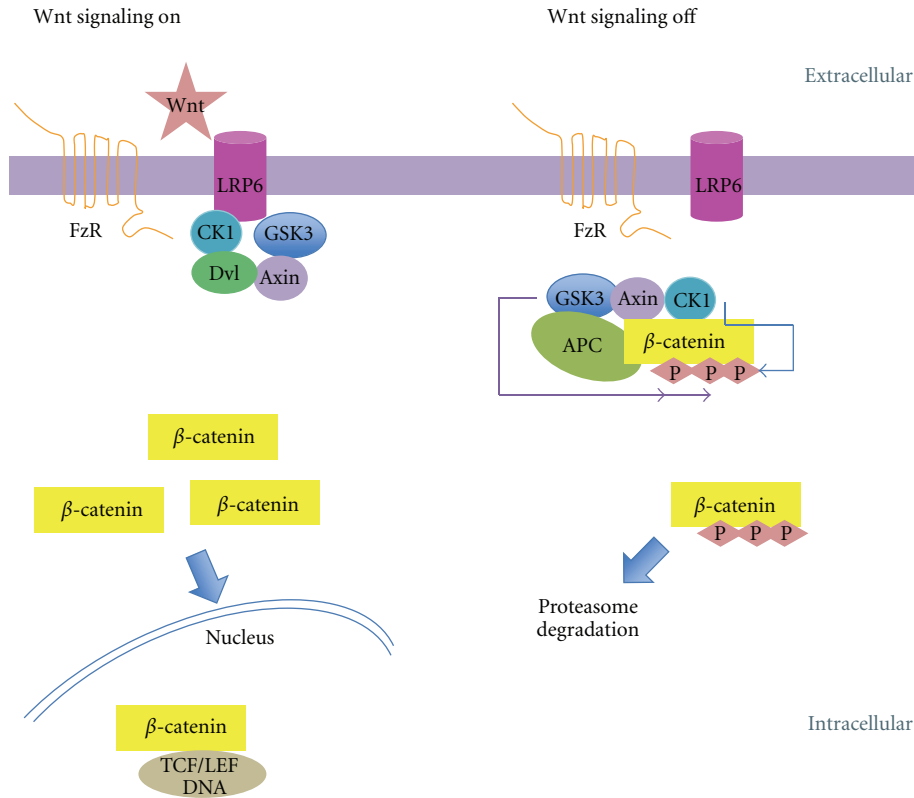


FIGURE 2: Canonical Wnt signaling and GSK3 regulation. Wnt activation through Frizzled receptor (FzR) induces destabilization of the protein complex composed of axin, adenomatous polyposis coli (APC) protein, β -catenin, casein kinase (Ck1), and GSK3, which results in GSK3 inhibition leading to the induction of β -catenin/TCF target gene expression. When Wnt signalling is off the GSK3/axin complex is not inhibited and β -catenin phosphorylated and is degraded by the proteasome machinery.

or diminished phosphatase and tensin homolog (PTEN) all activate the catalytic subunit of PI3K, which phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP₂) to phosphatidylinositol-3,4,5-trisphosphate (PIP₃) and activates phosphoinositide-dependent protein kinase-1 (PDK-1). Meanwhile, signaling proteins with pleckstrin homology (PH) domains accumulate at sites of PI3K activation on the inner surface of the plasma membrane through interactions between their PH domains and the phospholipid products of PI3K. Next, the serine-threonine kinase Akt/protein kinase B is recruited and phosphorylated by PDK-1, which stimulates the catalytic activity of Akt, in turn phosphorylating GSK3 to downregulate its activity.

The canonical Wnt pathway is also classically involved in negative regulation of GSK3. Although the role of Wnt proteins in mature neurons remains largely unexplored, recent data indicate that Wnts are important mediators of neuronal function, neuronal morphology, neurogenesis, and synaptic plasticity [50–52]. Interestingly, Wnt signaling has also been implicated in neurological disorders associated with developmental abnormalities, such as schizophrenia [53], as well as in chronic neurodegenerative diseases, such as AD [54]. Extracellular secreted Wnt proteins activate Frizzled receptor and/or the low-density lipoprotein-related protein 5 and 6 (LRP5/6) receptors, leading to the characteristic activation of the Wnt canonical pathway [55].

Due to Frizzled activation, the Dishevelled mammalian homolog Dvl1 is recruited, inducing destabilization of the protein complex composed of axin, adenomatous polyposis coli (APC) protein, β -catenin, and GSK3 β , which results in GSK3 β inactivation [56]. Inhibition of GSK3 β favors an increase in unphosphorylated β -catenin levels, allowing interaction with members of the lymphoid enhancer factor/T-cell factor (LEF/TCF) family of transcription factors and, as a consequence, promoting the expression of cell survival genes [57]. Although the molecular mechanism of GSK3 inhibition is not completely understood, Wnt signaling has recently been reported to trigger the sequestration of GSK3 from the cytosol to multivesicular organelles, preventing its interaction with cytoplasmic substrates [58] (Figure 2).

The outcome is different in the absence of the Wnt stimulation, which may occur due to lack of Wnt ligands or the presence of Wnt negative modulators, such as the extracellular protein Dickkopf-1 (Dkk1), which regulates the canonical Wnt signaling, or the secreted Frizzled-related protein, which modulates both canonical and noncanonical Wnt signaling [59]. Under these circumstances, GSK3 β is activated and able to phosphorylate its target proteins. Several regulators also target β -catenin/GSK3 β signaling. For example, the product of disrupted in schizophrenia 1 (DISC1) gene inhibits GSK3 β activity through a direct physical interaction, causing stabilization of β -catenins.

DISC1 loss-of-function in the dentate gyrus has been shown to result in reduced neural progenitor proliferation and to elicit hyperactive and depressive behaviors in mice [60], suggesting the involvement of GSK3 β overactivation in mental illnesses, such as depression and schizophrenia. Moreover, DISC1 function seems to be essential for neural progenitor proliferation in embryonic brains and in the dentate gyrus of adult brains through its ability to control GSK3 activity and to maintain β -catenin levels, which ultimately impacts the neural circuitry [60].

GSK3 β is also a downstream mediator of dopamine signaling via the dopamine D2 receptor/ β -arrestin 2/PP2A complex. In this signaling pathway, Akt activates neuregulin-1 signaling leading to inhibition of GSK3 β activity [61]. Interestingly, neuregulin-1 has been also implicated as schizophrenia risk factor [62].

In addition to the described role of GSK3 β in neurodevelopment, it has been recently found the potentiation of Notch signalling by PI3K through GSK3 β inhibition [63]. The Notch pathway has been implicated in controlling cell fate, differentiation, development as well as synaptic plasticity, learning and memory [64].

4. GSK3: A Switch for Cytoskeletal Reorganization and Synaptic Plasticity

Changes in neuronal morphology and plasticity are affected by GSK3-induced phosphorylation of proteins involved in the modulation of MT and neurofilament stabilization, which affect the cytoskeleton [65]. Among these proteins are tau, microtubule-associated protein 2 (MAP2), microtubule-associated protein 1B (MAP1B), collapsin response mediator protein 2, APC, axin, neurofilaments, kinesin light chain, and cytoplasmic linker protein [9, 16, 30, 31, 40, 53, 66–70].

The induction of polarity during neuronal development is essential for the establishment of circuits that support complex functioning [71, 72]. Subcellular location of the inactive form of GSK3 β varies depending on the state of neuronal polarization, as it moves from nonpolarized neurites to the neurite tip that will form the axon at the beginning of the differentiation process. Local inactivation of GSK3 is important to allow axonal growth concurrent with its activation in dendrites [73–76]. These mechanisms support the establishment of neuronal polarity, which is dependent on the stability and dynamism of the MT in each neuronal compartment [40, 53]. The relationship between GSK3 β and the microtubule stabilizing protein complex APC-mPar3, which are both present at the tip of the actively growing nascent axon, is important for the establishment of neuronal polarity. Shi and colleagues [74] have demonstrated that spatially regulated GSK3 activity in hippocampal neurons during development leads to axonal generation [74]. The inactivation of GSK3 at the nascent axon is required for mPar3 targeting through APC and kinesin-mediated transport at the plus end of the axonal MT [74].

Two further studies showed that GSK3 β inhibition in hippocampal neurons induces formation of multiple axons [75, 76]. However, the role of GSK3 in neurodevelopment remains only partially understood due to contradictory data;

other studies have found that GSK3 inhibition induces axonal spreading, reduces axonal elongation, and increases growth cone size, but it does not induce the formation of multiple axons [66, 68, 77–79].

One mechanism related to both synaptic reorganization and MT dynamics is Wnt signaling [80–82], which directs the growing axon towards the synaptic terminal. This process involves the reduction of axonal growth speed and the extension of axonal distal portions at the growth cone [83] until arborization forms functional synaptic endings where the presynaptic apparatus can be assembled. Transmembrane proteins, such as neuroligin/neurexin and cadherins, are also involved in this process and serve to regulate assembly on both sides of the synapse [52, 84]. Wnt proteins have a fundamental role in synapse formation, acting as retrograde signals that regulate assembly of the presynaptic apparatus [84]. Specifically, Wnt7a has a dual function in synaptic differentiation, promoting axon remodeling and increasing incorporation of synaptic proteins [66, 84]. These effects are linked to changes in the reorganization and dynamics (stabilization-destabilization) of MT, which are achieved through the canonical Wnt signaling, independent of the transcription pathway, in which GSK3 β activity is inhibited, and, consequently, the phosphorylation state of the axonal MAP1B is reduced [84–86]. The addition of Wnt7a to neuronal cultures reduces MAP1B phosphorylation and induces MT depolymerization from growing areas of the axon, promoting axonal growth cone enlargement and axonal spread [51, 66, 87]. The classical inhibition of GSK3 β by lithium chloride (LiCl) reproduces the effects of Wnt7a, inducing axonal arborization and widening and enlargement of the growth cone through remodeling of axonal MT during postnatal development of cerebellar cells [52, 87, 88]. On the other hand, it has been shown that Wnt7a increases the level of Synapsin I (SynI), which is known to be involved in synapse formation, as well as in the maturation and transport of synaptic vesicles in areas of growth [87, 89, 90]. Accumulation of SynI promotes both axonal remodeling and synaptogenesis during cerebellar development [87] and is mimicked by LiCl treatment [66, 88, 91].

GSK3 is also present in mature synapses [92], where its activity, along with that of cyclin-dependent kinase (Cdk5), participates in the recovery of synaptic vesicles during high neuronal activity. During this process, Cdk5 phosphorylates the GTPase dynamin I, and then GSK3 β phosphorylates the same dynamin I [93]. Both phosphorylation events are necessary and sufficient to trigger and maintain activity-dependent bulk endocytosis of vesicles [94].

As a result of controlling different morphofunctional aspects of adult brain plasticity, GSK3 also plays a role in long-term potentiation (LTP) [95, 96] and long-term depression (LTD). LTP might be considered the electrophysiological correlate of learning based on its synaptic mechanisms and long-lasting experience-dependent cortical circuits [97–99]. On the other hand, LTD has been suggested as a mechanism to enhance the signal-to-noise ratio of sensory input from stored memories [97]. Some studies have shown that GSK3 β inhibition upregulates and maintains LTP [24, 50, 91, 100–102], while GSK3 β remains active during

LTD [101]. In rat hippocampus, GSK3 β overactivation has been shown to impede LTP and affect synapses by decreasing both synaptic transmission and release of the presynaptic neurotransmitter glutamate [91]. This is regulated by proteins associated with synaptic vesicles, such as SynI [103–108], which is considered to be a synaptic plasticity marker [109, 110]. GSK3 β activation inhibits SynI expression after LTP induction and simultaneously disrupts SynI clustering, which results from elevated neuronal activity [91].

An other evidence that underscores the importance of GSK3 in brain plasticity is derived from experiments conducted in rat hippocampus by Gómez de Barreda and colleagues. The authors found that inhibitory phosphorylation of GSK3 at Ser9 increased at the time of LTP induction was maintained for up to one hour *in vivo* and was significantly higher in the hippocampal CA1 and dentate gyrus subregions, which are involved in learning and memory acquisition [39]. Transgenic mice overexpressing GSK3 showed reduced LTP induction [100]. These data confirm the significant participation of GSK3 in LTP regulation by enabling LTP when its catalytic activity is inhibited and preventing LTP when it is overactive. The inhibition of the two main signaling pathways (insulin/PI3K and Wnt) which induced an activation of GSK3 also prevents the induction of LTP [50, 64, 111–113].

GSK3 has been shown to induce LTD through presynaptic and postsynaptic mechanisms. In the presynaptic neuron, upregulation of GSK3 decreases the expression of SynI [91], which has been linked to a decrease in glutamate release [103]. In the postsynaptic neuron, GSK3 activation causes changes in levels of synapse-associated proteins [114, 115], evident as downregulation of the NR2A/B subunits of NMDA receptors and of the scaffolding protein postsynaptic density 93 (PSD93) [24, 91]. In addition, a transient activation of NMDA receptors and endocytosis of AMPA receptors occurs [116, 117], leading to the loss of GSK3 inhibition due to insufficient Ca²⁺ entry. This GSK3 inhibition is mediated by NMDA-PI3K-Akt signaling [112, 118]. Over-activity of GSK3 may also induce MT destabilization in dendrites and axons [80, 86, 119] (Figure 3).

Overexpression of GSK3 β in mice prevents the induction of LTP [100] and causes spatial memory deficits [120]. These data suggest that GSK3 β plays an essential role in memory formation through three general processes: (i) phosphorylation of substrates involved in synaptic remodeling, necessary for the establishment of new connections, (ii) turnover of cytoskeletal proteins such as MAPs, actin, and tubulin, promoting disassembly, a condition required for a proper synaptic reorganization, and (iii) involvement in the two major forms of synaptic plasticity in the brain, LTP, and LTD [121].

In summary, the functional consequence of GSK3 overactivation in mature neurons is inhibition of LTP and induction of LTD [101, 121], which could be linked to deficiencies of memory and learning characteristic of some neurological diseases, such as AD.

5. GSK3 and Alzheimer's Disease

AD represents a serious epidemiological problem, as it is now recognized as the most common age-related neurodegenerative disease. Evidence supports a role for GSK3 in producing some of the characteristic hallmarks of AD: extracellular accumulation of amyloid- β protein (A β) and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated forms of tau and inflammatory markers [122]. All of these effects contribute to synaptic and neuronal loss and memory decline [123, 124].

It has been proposed that overactivation of GSK3 in AD leads to inhibition of LTP and may partially explain the learning and memory deficits present early in this neurodegenerative disorder. On the other hand, changes in GSK3 activity may be a molecular link between the two main histopathological markers: A β overproduction and tau hyperphosphorylation [39, 46, 125, 126].

The NFTs that accumulate in AD are anomalous filamentous structures composed mainly of abnormal, hyperphosphorylated forms of tau protein [127]. Hence, numerous studies have focused on identification of the protein kinases and phosphatases regulating tau phosphorylation *in vivo*. GSK3 β was recognized as a primary kinase involved in tau phosphorylation, as was apparent from the first studies that termed it tau protein kinase-I [128]. Thus, GSK3 β has been identified as one of the major enzymes mediating tau hyperphosphorylation at the residues implicated in neurodegenerative tauopathies, including AD [129].

Normally, tau protein contains a total of 85 phosphorylatable sites: 45 Ser, 35 Thr, and 5 Tyr. Of these, 40 have been identified as phosphorylated in insoluble tau in AD brain: 28 Ser, 10 Thr, and 2 Tyr, and GSK3 β can phosphorylate 23 of these sites [130]. Although GSK3 β commonly needs priming phosphorylation of tau, three sites were recently found that can be phosphorylated by GSK3 β alone, without priming: Ser396, Ser400, and Ser404 [131]. Furthermore, initial phosphorylation of the Ser214 by cAMP-dependent protein kinase was shown to lead to the rapid modification of four additional sites by GSK3 β [131]. Studies in transgenic mouse models have shown that overexpression of GSK3 β results in neurodegeneration and have unequivocally demonstrated that GSK3 β phosphorylates tau in AD-related phosphoepitopes *in vivo* [93, 132, 133]. Moreover, co-overexpression of tau and GSK3 β synergistically increased tau phosphorylation and induced neuronal death in a transgenic model in *Drosophila* [134] while GSK3 inhibition reduces the phosphorylation and aggregation of tau [135, 136]. Similarly, tau hyperphosphorylation and neurodegeneration after GSK3 β overexpression are exacerbated by co-overexpression of tau with mutations characteristic of frontotemporal dementia with parkinsonism, associated with chromosome 17 (FDTP-17). This study also showed that tauopathy progression could be prevented by administration of a GSK3 β inhibitor at the first signs of pathology [133]. Tau knockout mice overexpressing GSK3 β show reduced hippocampal degeneration, indicating that tau partially contributes to the pathology observed in mouse brain [39]. Finally, GSK3 β inhibitors decrease tau phosphorylation and amyloid deposition in

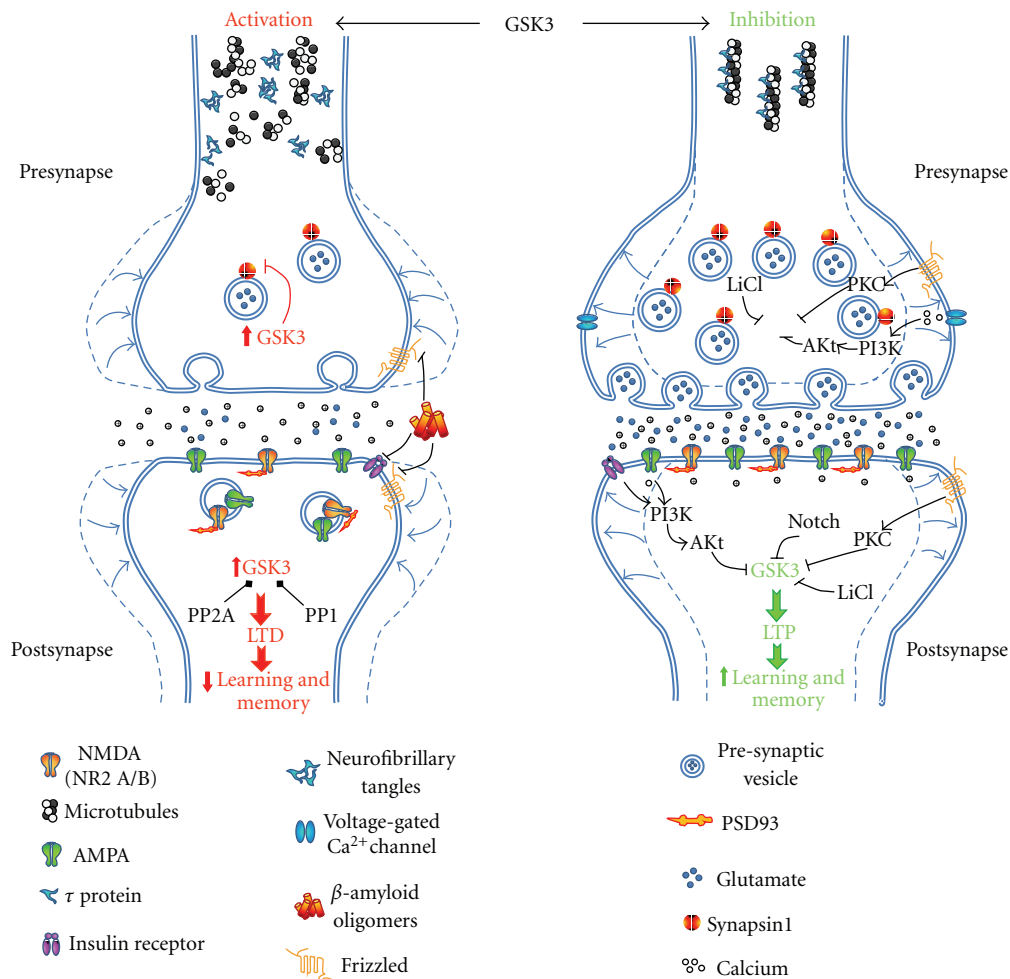


FIGURE 3: Schematic representation of pre- and postsynaptic mechanisms involved in neuronal plasticity and the role of GSK3. In the presynapse GSK3 activity decreases the expression of SynI reducing the release of glutamate while in postsynapses GSK3 transiently activates NMDA receptors leading to endocytosis of AMPA receptors and reduces the levels of PSD93 protein, favoring LTD. In contrast, Wnt and PI3K signaling pathways or pharmacological inhibition of GSK3 by LiCl supports the induction of LTP, facilitating learning and memory. GSK3 inhibition is also involved in axon and dendritic widening in both pre- and postsynaptic sites. Serine/threonine phosphatases PP1 and PP2A can activate GSK3 regulating phosphor-GSK3 levels through its dephosphorylation. GSK3 is important in the modulation of multiple signaling pathways including Notch pathway that plays an important role in different developmental processes. In AD, amyloid- β oligomers inhibit Wnt and insulin signaling pathways leading to activation of GSK3. In addition, GSK3 overactivation mediates τ hyperphosphorylation and microtubule destabilization.

a double transgenic mouse model coexpressing human mutant amyloid precursor protein (APP) and tau [137]. In brains of AD patients, GSK3 β colocalizes with NFT [138], and active GSK3 β is present in neuronal cytoplasm of neurons with tangle-like inclusions when abnormal tau hyperphosphorylation begins [139]. In fact, polymorphisms in GSK3 were recently reported to be risk factors for late-onset AD [140, 141].

Evidence suggests that GSK3 β regulates APP processing [126, 142], leading to increased production of A β . Neuronal exposure to A β increases GSK3 β activity through PI3K inhibition [143], causing a positive feedback loop. A β peptide can regulate GSK3 activity, acting as an insulin receptor antagonist and preventing activation of PI3K and Akt. In turn, the absence of activated Akt prevents the inhibitory

phosphorylation of GSK3, increasing its activity [144]. A β seems to interfere with the Wnt canonical pathway as well, leading to increased GSK3 activity [145]. Thus, deregulation of GSK3 in AD might be due, in part, to alterations in insulin and Wnt signaling. In the canonical Wnt signaling pathway, the gene for LRP6 coreceptor has been identified as a risk factor for late-onset AD in ApoE4-negative individuals [146]. Interestingly, it has been suggested that the Wnt pathway might be inhibited by ApoE protein, which likely binds to the coreceptor LRP5/6 [147]. Moreover, the ApoE4, implicated in sporadic AD [148], may activate GSK3 [46, 149].

Wnt dysregulation has also been implicated in AD. For example, protein Dickkopf-1 negatively modulates the canonical Wnt signaling pathway and thus activates GSK3. DKK1 colocalizes with NFT and dystrophic neurites in

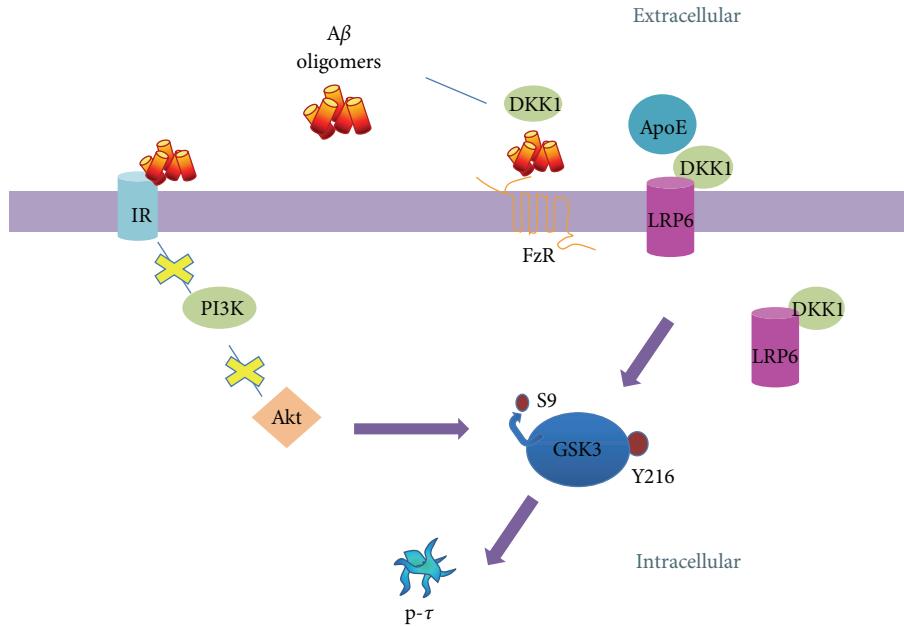


FIGURE 4: Proposed model of GSK3 activation by amyloid- β protein in AD. Amyloid- β oligomers bind to the insulin receptor and inhibit PI3K/Akt pathway, and Akt is unable to phosphorylate and inactivate GSK3. $A\beta$ also induces the expression of DKK1, which internalizes LRP6 receptor and inhibits Wnt signaling leading to GSK3 activation. $A\beta$ can bind to Frizzled receptor (FzR) and inactivate Wnt signaling as well. ApoE also inhibits this signaling pathway and activates GSK3. Tau hyperphosphorylation and NFT formation may result from GSK3 overactivation.

degenerating neurons of AD brains [150]. Moreover, using Wnt and PI3K signaling inhibitors, cultured cortical neurons have shown increased tau phosphorylation and morphological changes mediated by GSK3 β [151]. Taken together, this evidence suggests an important role for GSK3 in AD and supports the notion that GSK3 could be the link between amyloid and tau pathology [46] (Figure 4).

6. Concluding Remarks

GSK3 has attracted a great deal of interest due to the myriad of processes it controls. GSK3 is implicated in many fundamental functions, ranging from bioenergetics to developmental and plasticity events, particularly in the brain. Altered GSK3 activity in the brain negatively influences neuronal structure, which in turn may affect maintenance of neuronal circuits that support cognitive function. The use of therapeutic drugs to control GSK3 activity has been hampered by the variety of substrates targeted by this enzyme and the long-term ramifications of its downstream signaling. Future studies could focus on identifying spatiotemporal expression patterns of specific GSK3 isoforms in the brain with the goal of developing specific inhibitors for clinical use in devastating neurological diseases, such as AD.

Acknowledgments

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