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# Lithium inhibits GSK-3 through disruption of Striatal β-Arrestin, PP2A, and Akt Signaling

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## Abstract

β-Arrestin, PP2A, and Akt form a signaling complex that affects the activation of GSK-3. GSK-3 affects the pathway leading to neurodegenerative diseases. Lithium is a known mood stabilizer which exhibits a direct or indirect inhibition of GSK-3. GSK-3 is the link between neurodegeneration and the mitigating potential of lithium via the direct and indirect inhibition of this enzyme. This review reveals the mechanisms associated with lithium neuroprotection and the synergies between β-arrestin, PP2A, AKT, and GSK-3, the limiting effects on the progression of neurodegeneration.

**Keywords:** β-Arrestin; Lithium; GSK-3; PP2A; Neuroprotection

## 1.0 Introduction

### 1.1 Neurodegenerative Diseases

Neurodegenerative diseases represent a major threat to human health (Gitler *et al.*, 2017). These disorders are increasingly prevalent and dependent on age, prominently among the elderly population in recent years (Heemels, 2016). Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and spinocerebellar ataxias. These diseases are diverse in their pathophysiology–with some causing memory and cognitive impairments and other factors affecting a person's ability to move, speak, and breath (Abeliovich and Gitler, 2016; Taylor *et al.*, 2016). These diseases are the consequence of misfolding and dysfunctional trafficking of proteins. Mitochondrial dysfunction, oxidative stress, and/or environmental factors strongly associated with age have also been implicated in neurodegeneration (Sheikh *et al.*, 2013). There is evidence that suggested that these disorders are limited to diverse factors such as (a) abnormal

protein dynamics with defective protein degradation and aggregation, (b) oxidative stress and free radical formation, (c) impaired bioenergetics and mitochondrial dysfunction, and (d) exposure to metal toxicity and pesticides.

### 1.2 β-Arrestin

β-Arrestins are cytoplasmic proteins with ubiquitous expression throughout the body, and due to their critical role in regulating G-protein-coupled receptors (GPCRs), they have emerged as one of the important nodes in cellular signaling pathways (Lefkowitz and Shenoy, 2005). β-arrestin modulation of GPCR function includes termination of G protein-dependent signaling, initiation of ß-arrestin-dependent signaling, receptor trafficking to degradative or recycling pathways, receptor transactivation, transcriptional regulation, and localization of second messenger regulators (Bond *et al.,* 2019). A key feature of β-Arrestins is their ability to bind a large number of cellular proteins and facilitate the formation of multi-protein signalosomes in the cellular context (DeWire *et al.,* 2007). β-Arrestin, which are nonvisual arrestins, are referred to as β-Arrestin 1 and β-Arrestin 2 (Fan, 2014). β-arrestins which are scaffolding and adaptor proteins, play key roles by interacting with several molecules implicated in the transduction of signal and cellular trafficking, increasing functional and spatial proximity among molecules, thereby enhancing inter-protein interactions with the formation of multi-protein complexes (Lefkowitz *et al.,* 2006).

The interacting tendency of β-arrestins with related proteins to facilitate receptor endocytosis and signaling is regulated by phosphorylation and ubiquitination which are posttranslational modifications. Mammalian arrestins thrive in the cytosol in constitutively phosphorylated form and are dephosphorylated by interaction with activated 7TMRs upon binding at the plasma membrane (DeWire *et al.,* 2007). For β-arrestin 1, serine 412 is the site of extracellular signal-regulated kinase (ERK) ½-mediated phosphorylation (Lin *et al.,* 1999). In contrast, for β-arrestin2, which is phosphorylated by casein kinase II, threonine 383 is the primary phosphorylation site, and serine 361 represents a secondary site (Kim *et al.,* 2002; Lin *et al.,* 2002). Both β-arrestins are polyubiquitinated, and this posttranslational modification is required for their endocytic function (Shenoy *et al.,* 2001). Ubiquitination is triggered by the interaction of β-arrestins with an activated receptor (Herranz *et al.,* 2005). Ubiquitination is sequentially catalyzed by three enzymes. The first step of catalysis is the formation of a high-energy thioester bond by E1 which is a ubiquitin-activating enzyme, activating the COOH-terminal glycine residue of ubiquitin. Followed is the transfer of activated ubiquitin to an active-site cysteine residue in an E2 (ubiquitin-carrying enzyme). The final reaction is catalyzed by ubiquitin-protein ligase E3, which ligates the COOH terminus of ubiquitin to the ε-amino group of a lysine residue of the substrate protein (DeWire *et al.,* 2007).

### 1.3 Protein Phosphatase Type 2A

Protein phosphatase type 2A (PP2A) is a major serine-threonine protein phosphatase in all eukaryotic cells (Lechward *et al.,* 2001). Structurally, it is constituted of three different subunits, namely catalytic subunit (PP2Ac), structural scaffold subunit (PP2A-A), and a regulatory subunit (PP2A-B) (Nematullah *et al.,* 2018). It plays a key role in several regulating cellular functions such as neural growth, replication, transcription, translation, cell cycle, cell transformation, metabolic pathways including glycolysis, lipid metabolism, and catecholamine synthesis (Tung *et al.,* 1985).

PP2A is responsible for controlling stimulus-activated protein kinases. Upon cell stimulation, specific kinases are transiently phosphorylated and activated. Several of these protein kinases are substrates for PP2A. This phosphatase

appears to be a major kinase phosphatase in eukaryotic cells that down-regulates activated protein kinases (Millward *et al.,* 1999). PP2A controls the activities of several major protein kinase families, in particular protein kinase B (PKB also known as Akt), protein kinase C, calmodulin-dependent kinases, MAP kinases, and cyclin-dependent kinases (Lechward *et al.,* 2001) thereby affecting neuronal growth (Janssens and Goris, 2001). There are two main functions of PP2A (Smith and Walker, 1996; Shi, 2009): (i) the regulation of vital metabolic pathways and (ii) several key signal transduction pathways are characterized by cascade events with proteins undergoing reversible phosphorylation. PP2A preferentially dephosphorylates Akt at Thr308 residue, but under certain conditions, it can also dephosphorylate the Ser473 residue (Liao and Hung, 2010).

### 1.4 Protein Kinase B or Akt

Protein kinase B (PKB, also known as Akt) is a signaling protein that plays a central role in the regulation of metabolism, cell survival, motility, transcription, and cell-cycle progression (Fayard *et al.,* 2005). Akt belongs to the super protein kinase family named AGC after the kinases members that share structural homology within their catalytic domain and have similar mechanisms of activation (Song *et al.,* 2005). The phosphorylation of the regulatory threonine residue, Thr308 residue activates Akt (Song *et al.,* 2005). Akt exists in three different isoforms conserved in mammalian genomes: Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ) (Manning and Toker, 2017). Akt1 is ubiquitously expressed at high levels (Coffer and Woodgett, 1991; Jones *et al.,* 1991b; Bellacosa *et al.,* 1993). In contrast, Akt2 is highly expressed in insulin-sensitive tissues including the liver, skeletal muscle, and adipose tissue (Jones *et al.,* 1991a; Konishi *et al.,* 1994). The expression of Akt2 is drastically increased during the differentiation of adipose tissue and skeletal muscle (Hill *et al.,* 1999; Vandromme *et al.,* 2001). Akt3 is expressed most highly in the brain and testis and exhibits lower levels of expression in intestinal organs and muscle tissue (Nakatani *et al.,* 1999). All three Akt/PKB isoforms consist of a conserved domain structure: an amino-terminal pleckstrin homology (PH) domain, a central kinase domain, and a carboxy-terminal regulatory domain that contains the hydrophobic motif, a characteristic of AGC kinases (Song *et al.,* 2005). Akt is a critical protein kinase that modulates apoptotic and survival pathways (Chakraborty, 2008). Akt promotes cell survival by mediating the cellular growth factors and blocking apoptosis by the inactivation of pro-apoptotic proteins.

Akt plays a key role in signaling as it is a downstream component in phosphoinositide (PI) 3-kinase signaling, which is activated upon (1) autophosphorylation of receptor tyrosine kinases induced by ligands (such as insulin or other growth factors), (2) stimulation of G-protein-coupled receptors, or (3) activation of integrin signaling (Foster *et al.,* 2003; Wymann *et al.,* 2003; Fayard *et al.,* 2005).

### 1.5 Glycogen Synthase Kinase 3

The glycogen synthase kinase 3 (GSK-3) family of serine-threonine kinases is composed of two isoenzymes/paralogous proteins GSK-3α and GSK-3β, which were originally identified for their role in insulin receptors signaling (Cross *et al.,* 1995; Freland and Beaulieu, 2012). The main structural difference between GSK-3α and GSK-3β isoforms lies in the N- and C- terminal regions, while their sequence within the kinase domain are highly homologous. Although GSK-3α and GSK-3β are highly homologous within their kinase domains and display similar biochemical and substrate properties, their functional roles are not always identical (Liang and Chuang, 2006). In addition, GSK-3β plays a more important role than GSK-3α in mediating spontaneous neuronal death in extended cultures

(Liang and Chuang, 2007). GSK-3 is considered to be constitutively active under non-stimulated basal conditions (Chuang *et al.*, 2011). It is primarily regulated through inhibition of its activity either by phosphorylation or the regulation of its incorporation into protein complexes. GSK-3 also has the ability to promote self-activation through enhancing phosphatase activity which removes its own N-terminal inhibitory phosphate groups (Zhang *et al.*, 2003).

## 2.0 Activation and Regulation of β-Arrestin, PP2A, AKT and GSK-3

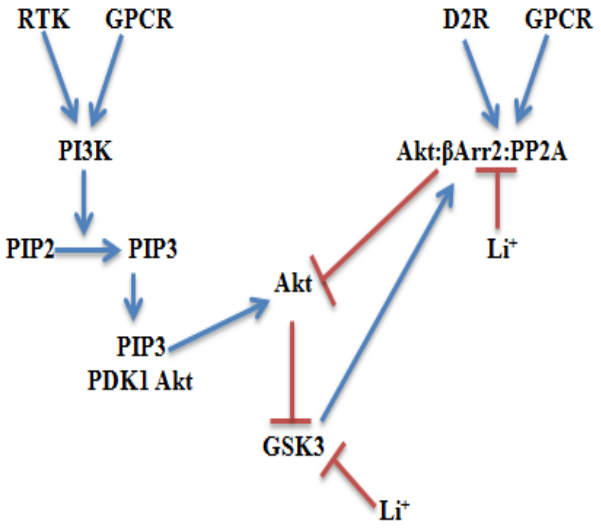


**Figure 1**: Schematic representation of signaling pathways regulating the activity of brain GSK-3 and its regulation by lithium (Freland and Beaulieu, 2012).

This series of reactions are initiated by the stimulation of receptor tyrosine kinases (RTK) or G-protein-coupled receptors (GPCR) leading to plasma membrane recruitment and activation of one or more isoforms of the class phosphoinositide 3-kinase (PI3K) family. PI3K then in turn phosphorylates Phosphatidylinositol 4,5-bisphosphate (PIP2) into Phosphatidylinositol (3,4,5)-triphosphate (PIP3). Akt is not directly activated by PIP3, which alters Akt configuration by binding to its PH region and recruits it to the plasma membrane allowing phosphoinositide-dependent kinase-1 (PDK1) to phosphorylate at Thr308 residue in the kinase domain. The activation of PI3K results in the phosphorylation of two key residues on Akt1, T308 in the activation, or T-loop, of the catalytic protein kinase core, and S473 in a C-terminal hydrophobic motif (Alessi *et al.*, 1996). Phosphorylation of both residues is required for maximal activation of the kinase. The regulation also occurs on corresponding residues in Akt2 (T309 and S474) and Akt3 (T305 and S472). The Phosphoinositide-dependent protein kinase 1 (PDK1) was discovered for its ability to phosphorylate Akt1 at T308, which is required for Akt activity (Alessi *et al.*, 1997; Stokoe *et al.*, 1997). Relocalization of both Akt and PDK1 to membrane sites of PIP3 synthesis induces conformational changes, providing access of PDK1 to Akt for phosphorylation of T308 (Manning and Toker, 2017). This phosphorylation of Akt by PDK1 leads to the activation of Akt. Phosphorylation of N-terminal serine residues of GSK-3 isoforms by activated Akt results in GSK-3 inactivation.

Using the D2 class of dopamine receptors, Beaulieu and colleagues (Beaulieu *et al.*, 2005) found that dopamine stimulates the formation of a signaling module consisting of β-arrestin2, Akt, and its negative regulator, PP2A. This signaling complex favors the dephosphorylation of Akt on the T308 resulting in the inactivation of Akt. When Akt is inactivated, its inhibitory effect on GSK-3 is relieved. Research shows that GSK-3 can promote its activation by stabilizing the Akt, β-arrestin 2, and PP2A signaling complex (O'Brien *et al.*, 2011). In mice lacking β-arrestin2, dopamine was unable to regulate Akt signaling, as PP2A and Akt could no longer interact. Furthermore, behavioral effects associated with dopamine administration, such as increased locomotor activity and wall climbing, were lost in these mice, demonstrating the

importance of β-arrestin2 in mediating these events (Beaulieu *et al.*, 2005).

## 2.0 Neurochemistry of Lithium

Lithium, popular for its function as a mood stabilizer has been used alone or in combination for the treatment of bipolar disorder, schizophrenia, depression, and other mental illnesses. Lithium is an alkali metal that is used medically under the form of a cationic salt Li+ in association with carbonate or citrate (Freland and Beaulieu, 2012). It is the only treatment that has shown efficacy for the treatment of acute mania and acute depression as well as prevention of recurrent mania and depression (Dunner, 2003; Young, 2009).

Lithium, when in high concentration can inhibit GSK-3 directly (Jope, 2003). As a hypothesis, the direct inhibition of GSK-3 by lithium occurs because Li+ ions act as a competitive inhibitor for the binding of the cofactor magnesium to GSK-3 since they share similar ionic radii (Ryves and Harwood, 2001). An experiment carried out by Beaulieu and colleagues (Beaulieu *et al.*, 2008) indicated that magnesium is a cofactor for the interaction of Akt and βArr2. Furthermore, this suggests that lithium competition with magnesium can affect not only enzymatic activity but also the stability of higher-order protein complexes, thus providing a potential mechanism for the destabilization of the Akt:βArr2:PP2A complex by lithium.

Apart from the direct inhibition, lithium can still inhibit GSK-3 indirectly by activating Akt. Lithium can also act by disrupting the Akt, β-arrestin 2, and PP2A signaling complex in striatal homogenates, thereby, providing a mechanism for the activation of Akt (Beaulieu *et al.*, 2008). The inhibition of GSK-3β is the main mechanism of lithium's neuroprotective actions (Li *et al.*, 2002).

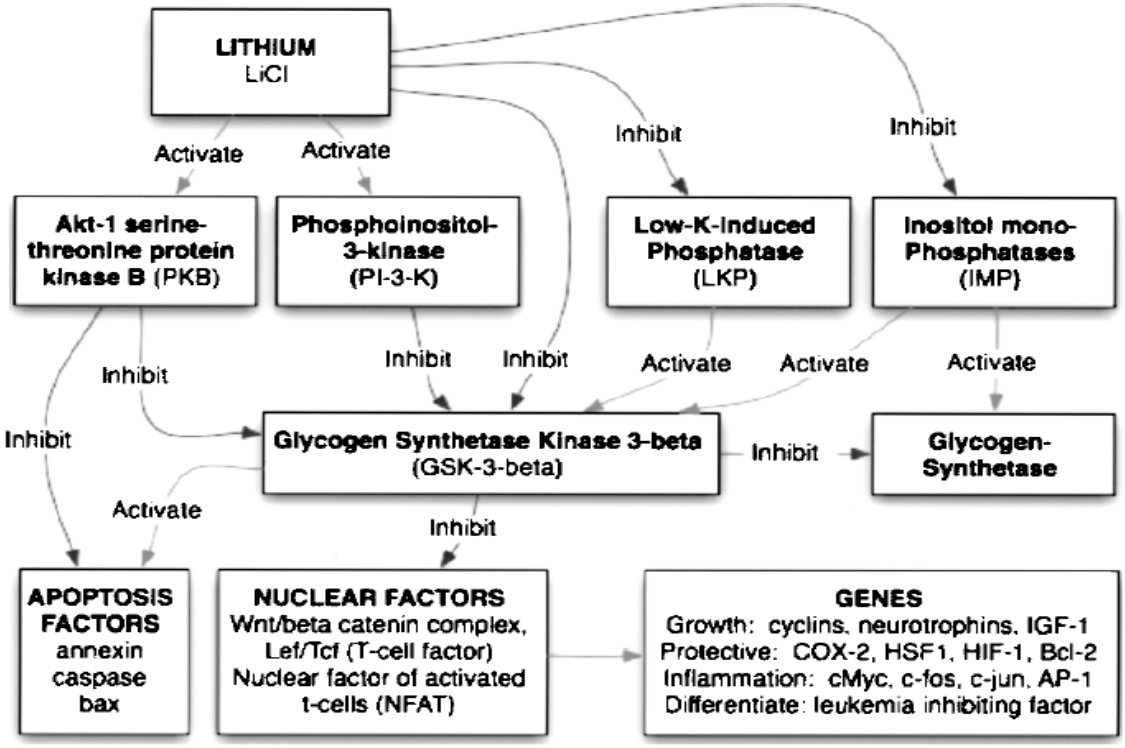

Figure 2: Effects of Lithium (Young, 2009).

Many lithium-sensitive behaviors in mice require β-arrestin-2, and assembly in the striatum of a complex that includes β-arrestin-2, Akt, and PP2A is sensitive to lithium. β-Arrestin-2 recruits PP2A to dephosphorylate and inactivate Akt. As Akt phosphorylates and inactivates GSK-3, assembly of this complex is predicted to enhance GSK-3 activity. Lithium interferes with the stability of this β-arrestin complex, and, by preventing PP2A-dependent dephosphorylation of Akt, enhances Akt-mediated inhibition of GSK-3 (O'Brien *et al.,* 2011).

## 3.0 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and behavioral change (Muazzam *et al.,* 2016). Alzheimer's disease can be characterized by three primary groups of symptoms (Burns and Iliffe, 2009). The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (that is, loss of higher-level planning and intellectual coordination skills). The second group comprises psychiatric symptoms and behavioral disturbances—for example, depression, hallucinations, delusions, agitation—collectively termed non-cognitive symptoms (Burns *et al.,* 1990). The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided) (Burns and Iliffe, 2009). Two findings characterize AD, neurofibrillary tangles (NFTs), and amyloid plaques, and both are promoted by GSK-3 (Snitow *et al.,* 2021). Abnormal tau phosphorylation and the formation of neurofibrillary tangles are the main pathological hallmark of AD, and several kinases including GSK-3β, Akt/PKB, ERK, and JNK phosphorylate the tau protein (Plattner *et al.,* 2006; Henriques *et al.,* 2015). Elevated GSK-3β activity is directly linked to increased levels of Aβ production and deposits, tau hyperphosphorylation, and the formation of neurofibrillary tangles (Reddy, 2013; Hernandez *et al.,* 2012). GSK-3β is rendered inactive when it is phosphorylated at Ser9 by phosphorylated Akt, and therefore an upregulation of Akt may contribute to a decrease in AD progression. The elevation of Akt activity has emerged as an effective strategy with which to prevent progressive neuronal death in neurological diseases (Nitulescu *et al.,* 2018). In the brains of patients with Alzheimer's disease (AD), decreased PP2A activities were observed, which is suggested to be involved in neurofibrillary tangle (NFT) formation, disturbed amyloid precursor protein (APP) secretion, and neurodegeneration in the AD brain (Liu and Tian, 2009).

## 4.0 Parkinson's Disease

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and widespread presence of alpha-synuclein (aSyn), an intracellular protein (Radhakrishnan and Goyal, 2018). Oxidative stress is a major cause of Parkinson's disease pathogenesis, inducing neuronal cell death and apoptosis by intracellular calcium overload, lipid peroxidation, DNA damages, and excitotoxicity. The activation of Akt has been shown to efficiently protect neurons or neuronal cells from oxidative stress and is an established target of drug design (Nitulescu *et al.,* 2018). GSK-3 phosphorylates α-synuclein and tau in Parkinson's disease, which leads to the development of the neurotoxic aggregates that drive the disease (Duka *et al.,* 2009).

## 5.0 Conclusion

The inhibition of GSK-3β is the main mechanism of lithium's neuroprotective chemistry (Li *et al.,* 2002). GSK-3β has been shown to play key roles in the progression of neurodegeneration (Lazzara

and Kim, 2015). The inhibition of GSK-3 by lithium correlates with reduced tauopathy and degeneration in vivo (Noble *et al.*, 2005). Lithium-only treatment may not be a suitable therapeutic for neurodegenerative diseases due to inconsistent efficacy and potential side-effects (Lazzara and Kim, 2015), however, the use of lithium as a means of reducing the progression of neurodegeneration is advisable. Further research should be considered on the combinatorial effects of lithium with known psycho-therapeutic drugs.

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